

**REMARKS**

This paper is being filed in response to the Office Action dated November 7, 2002 that was issued in connection with the above-identified patent application. Applicants request a one-month extension of time and enclose the fee required pursuant to 37 C.F.R. §1.17(a)(1). Applicants also enclose herewith a Supplemental Information Disclosure Statement, Form PTO-1449, and the fee required pursuant to 37 C.F.R. §§1.17(p) and 1.97(c). Applicants further enclose herewith a Second Substitute Sequence Listing in paper and computer readable form. Applicants respectfully request reconsideration of the instant application in view of the amendments and remarks presented herein.

Claims 39-86 were pending. Claims 52, 57-79, 80-81, and 83-84 have been withdrawn from consideration. Claims 39-41, 52, 54, 57-79, 80-81, and 83-84 have been cancelled herein without prejudice and Claims 42-49, 53, 55-56, 82, and 85-86 have been amended. The amendments are supported by the instant specification and, therefore, do not constitute new matter. Upon entry of the instant Amendment, claims 42--51, 53, 55-56, 82, and 85-86 will be pending.

Rewritten specification paragraphs and claims appear in the preceding "IN THE SPECIFICATION" and "IN THE CLAIMS" sections respectively. Attached hereto is a marked-up version of the changes made by the instant amendment. The attached pages are captioned "VERSION WITH MARKINGS TO SHOW CHANGES MADE" and are included pursuant to 37 C.F.R. §1.121(c)(ii). Should any discrepancies be discovered, the version presented in the preceding "IN THE SPECIFICATION" and "IN THE CLAIMS" sections shall take precedence.

### *Sequence Letter*

The Examiner has objected to the specification as containing sequence disclosures, yet allegedly failing to comply with 37 C.F.R. §§1.821-1.825. Applicants traverse this objection and assert that the specification, as amended herein, complies with 37 C.F.R. §§1.821-1.825. Applicants, therefore, respectfully request withdrawal of this objection.

Applicants submit herewith a Second Substitute Sequence Listing in paper and computer readable form. The undersigned hereby states that the content of the paper and computer readable copies of the Second Substitute Sequence Listing submitted in accordance with 37 C.F.R. §1.821(c) and (e), are the same. The undersigned hereby also states that the content of the paper and computer readable copies of the Second Substitute Sequence Listing, submitted in accordance with 37 C.F.R. §1.821(g), herein does not include new matter.

Applicants Second Substitute Sequence Listing corrects typographical errors in the sequences presented in the original application. Applicants enclose herewith five sequence alignments (Alignments 1-5) for the Examiner's review wherein corrections are highlighted. In each case, the Examiner's attention is respectfully invited to the aligned sequences which provide support for the changes.

### *Drawings*

The Examiner has objected to the drawings on the grounds that the Brief Description of the Drawings allegedly fails to refer to multiple frames. Applicants assert that the Brief Description of the Drawings, as amended herein, fully complies with MPEP §608.01(f) and, therefore, respectfully request withdrawal of this objection.

**Claims Are Draw to Statutory Subject Matter**

The Examiner has rejected claims 39-43, 45-47, and 55-56 under 35 U.S.C. §101 as allegedly reading on a product of nature. Applicants traverse this rejection and assert that the claims are drawn to statutory subject matter. Applicants assert that it is unnecessary to recite "isolated" or "purified" in the instant claims because a polypeptide having the amino acid sequence of SEQ ID NO:8 and nucleic acids which encode such a polypeptide do not occur in nature. *See e.g.* Example 8 and Figures 4A and 4B. Since the engineered molecules having the sequences of SEQ ID NOS:7 and 8 respectively display the requisite "hand of man and do not otherwise occur in nature, Applicants respectfully request withdrawal of this rejection.

The Examiner has also rejected claims 43 and 48-51 under 35 U.S.C. §101 and 35 U.S.C. §112, first paragraph as allegedly unsupported by a specific and substantial asserted utility or a well established utility.

Applicants traverse this rejection and assert that the claims, as amended herein, are drawn to statutory subject matter having specific, substantial, and credible utility. The risks and consequences of human exposure to botulinum neurotoxin are readily apparent to those of ordinary skill in the art and, indeed, to society at large. Applicants assert that the nucleic acids, the polypeptides, and the methods of the invention have use, *inter alia*, in immunization of humans and mammals against botulinum neurotoxin toxicity. *See e.g.* Example 10, page 41, lines 8-24 and Table 6. Therefore, Applicants respectfully request withdrawal of these rejections.

**Claims Are Supported by Sufficient Description**

Claims 39-42, 43, 44-51, 55-56, 82, and 85-86 have been rejected under 35 U.S.C. §112, first paragraph as allegedly lacking sufficient description to convey to one skilled in the art that Applicants were in possession of the invention at the time of filing. The Examiner alleges that the description does not support the breadth of claims drawn to a genus of nucleic acids where only one species is provided and the claim(s) do not recite a specific function of the nucleic acids.

Applicants traverse this rejection and assert that the claims, as amended herein, are fully supported by the description such that one of ordinary skill in the art would readily appreciate that Applicants were in possession of the invention on or before the filing date. Claims 39-41 have been cancelled rendering rejection of these claims moot. Claim 43 has been amended to independent form. Support for this amendment may be found in the specification as filed at, *inter alia*, Example 8 and Figure 4. Therefore, Applicants respectfully request withdrawal of this rejection.

**Claims Are Enabled by the Description**

Claim 54 has been rejected under 35 U.S.C. §112, first paragraph as drawn to subject matter that allegedly is not described in the specification in such a way as to enable one skilled in the art to make and use the invention. The Examiner has alleged that the recombinant organism of claim 54 does not produce, express, or comprise a coding sequence for botulinum neurotoxin.

Claim 54 has been cancelled. Applicant's response to this rejection is directed to claim 53. Applicants traverse this rejection and assert that claim 53, as amended herein, is fully enabled by the specification as filed. The transfected cell of claim 53 comprises "an expression vector comprising a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8." Moreover, the method of claim 53 comprises culturing this organism "under conditions wherein the nucleic acid is expressed". This claim has ample support in the specification at, *inter alia*, Examples 3 and 8. Therefore, Applicants respectfully request withdrawal of this rejection.

**Claims Are Clear and Definite**

Claims 39-51, 53-56, 82, 85, and 86 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly reciting non-elected inventions. Applicants assert that the claims, as amended herein, do not recited non-elected subject matter.

Claims 39-41 have been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for use of the phrases "encodes the carboxy-terminal portion" (claim 39), "is capable of" (claim 39), "the gram negative bacteria is Escherichia coli" (claim 40), and "the yeast is Pichia pastoris". Applicants respectfully submit that these rejections are moot since claims 39-41 have been cancelled.

Claim 43 has been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly reciting neither a function nor a specific structure. Applicants traverse this rejection and assert that claim 43, as amended herein, recites both a structure and a function. Applicants assert further that this claim is broader than the original claim in that it recites SEQ ID NO:8 rather than SEQ ID NO:7.

Claim 44 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "wherein the nucleic acid is a synthetic nucleic acid". Claim 44, as amended herein, does not recite this phrase.

Claims 45 and 46 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly lacking antecedent basis for the recited expression control sequence. Applicants have amended claim 45 to recite "further comprising" according to the Examiner's suggestion.

Claim 48 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the word "organism" in reference to mammalian cell lines. Claim 48 has been amended herein to replace the word "organism" with the word "cell".

Claim 48 has also been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "transfecting an organism with the nucleic acid of claim 39". The Examiner has alleged that the nucleic acid of claim 39 is defined as any portion of the carboxy-terminus of botulinum neurotoxin heavy chain and therefore, is not required to encode a botulinum neurotoxin. The Examiner has requested clarification as to what is encoded by the nucleic acid and what is expressed therefrom.

Applicants traverse this rejection and assert that claim 48, as amended herein, clearly sets forth what is encoded by the nucleic acid and what is expressed therefrom. Applicants respectfully invite the Examiner's attention to the phrase "a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8" in relation to what is encoded by the nucleic acid. In addition, Applicants respectfully invite the Examiner's attention to the phrase "comprising at least one immunogenic epitope" in relation to what is expressed. Applicants assert that one of ordinary skill in the art would recognize that

while all or substantially all of the nucleic acid may be expressed by the recombinant cell of claim 48, the polypeptide comprising a carboxy-terminal portion of the heavy chain of botulinum neurotoxin serotype B comprising at least one immunogenic epitope constitutes less than the full-length of SEQ ID NO:8. In view of these and other amendments, Applicants assert that claim 48 is clear and definite.

Claim 49 has been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly lacking antecedent basis for the term "protein". The Examiner has alleged that it is unclear whether the carboxy-terminal is a part of the "protein". The Examiner has also alleged that it is unclear what "protein" is being recovered. Applicants traverse this rejection and assert that claim 49, as amended herein, satisfies the requirements of 35 U.S.C. §112, second paragraph.

Claim 53 has been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly failing to recite method steps that correspond with the preamble. The Examiner has alleged that claim 53 fails to recite expression or isolation of a heavy chain portion or preparation or formulation of an immunogenic composition. Claim 53 has also been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "in expressible form".

Applicants traverse this rejection and assert that claim 53, as amended herein, claims the subject method in a manner that complies with 35 U.S.C. §112, second paragraph. Applicants respectfully invite the Examiner's attention to the phrase "recovering from said transfected cell at least one insoluble polypeptide" recited by amended claim 53. In view of this phrase and other amendments, Applicants assert that the method steps of amended claim 53 correspond to the preamble. In addition, amended claim 53 does not recite the phrase "in expressible form".

Claim 54 has been rejected under 35 U.S.C. §112, second paragraph as allegedly indefinite for its use of the phrase "recovering an insoluble protein fraction". This rejection will be moot upon entry of the instant Amendment whereby claim 54 has been cancelled.

Claims 85 and 86 have been rejected under 35 U.S.C. §112, second paragraph as indefinite for allegedly lacking antecedent basis for the term "protein". Claims 85 and 86 have been amended to recite "polypeptide" as is clearly recited in amended claim 43.

For the foregoing reasons, Applicants believe that the claims comply with the requirements of 35 U.S.C. §112, second paragraph and, therefore, respectfully request withdrawal of these rejections.

### **Claims Are Novel over the Cited Documents**

Claims 43, 48, and 53 are independent claims. Claims 42, 44-47, 55-56, 82, and 85-86 depend from claim 43. Claims 49-51 depend from claim 48. For a reference to anticipate, it must teach each and every element of the subject claim. *See e.g.* MPEP §2131. Since a dependent claim is to be construed to include all of the limitations of the claim from which it depends, *see e.g.* 37 C.F.R. §1.75(c), a document that fails to teach an element of an independent claim necessarily fails to teach an element of an attendant dependent claim. Therefore, Applicants will respond to the following rejections primarily as they apply to claims 43, 48, and 53.

#### **1. Campbell Does Not Teach SEQ ID NO:8**

Claims 39-47, 54-56, and 82-86 have been rejected under 35 U.S.C. §102(a) as allegedly unpatentable over Campbell KD et al., 1993, *J. Clin. Microbiol.* 31(9):2255-2262 (hereinafter "Campbell"). The Examiner has alleged that Campbell teaches a nucleic acid



sequence of the carboxy-terminal of a botulinum neurotoxin of SEQ ID NO:7 and encodes a portion of SEQ ID NO:8.

Applicants traverse this rejection and assert that the claims, as amended herein, are not anticipated by Campbell. This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein. Applicants note that the Examiner has included non-elected claims 83 and 84 in this rejection. Applicants suspect that this is a simple clerical error, but respectfully request clarification.

Claims 43, 48, and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope". Applicants respectfully invite the Examiner's attention to Alignments 6-9 attached hereto, which show that Eklund 2B and NCTC 7273 of Campbell are not the same as SEQ ID NOS:7 and 8 of the present invention. Therefore, since Eklund 2B and NCTC 7273 of Campbell fail to teach SEQ ID NO:8 herein, Campbell fails to anticipate each and every element of claims 43, 48, and 53. Consequently, Applicants respectfully request withdrawal of this rejection.

## **2. Smith 1998 Does Not Teach SEQ ID NO:8**

Claims 39, 41, 48, and 51 have been rejected under 35 U.S.C. §102(a) as allegedly unpatentable over Smith LA, 1998, *Toxicon* 36(11):1539-1548 (hereinafter "Smith 1998"). The Examiner has alleged that Smith 1998 discloses a nucleic acid encoding a *Clostridium botulinum* type B heavy chain capable of being expressed in *Pichia pastoris*. The Examiner has further alleged that Smith 1998 discloses a method of producing an immunogenic composition comprising culturing a recombinant *Pichia pastoris* cell and recovering the expressed heavy chain polypeptide.

Applicants traverse this rejection and assert that Smith 1998 does not anticipate the claimed invention. This rejection will be moot as to claims 39 and 41 upon entry of the instant Amendment in view of the cancellation of these claims herein. Claim 48, as amended herein, recites “transfecting a cell with a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope”. Smith 1998 does not teach the amino acid sequence of SEQ ID NO:8. Since Smith 1998 does not teach each and every element of the claimed invention, Applicants respectfully request withdrawal of this rejection.

### **3. Halpern Does Not Teach SEQ ID NO:8**

Claims 39-47, 54-56, and 82-86 have been rejected under 35 U.S.C. §102(a) as allegedly unpatentable over Halpern JL et al., 1993, *J. Biol. Chem.* 268(15):11188-11192 (hereinafter “Halpern”). The Examiner has alleged that Halpern discloses a nucleic acid that has a nucleotide sequence encoding the carboxy-terminal portion of a botulinum neurotoxin, wherein the nucleic acid encodes an amino acid sequence that is conserved across Clostridial neurotoxins including serotype B. The Examiner has further alleged that Halpern discloses a nucleic acid encoding the amino acid sequence Asp-Glu-Gly-Trp-Thr. In addition, Halpern allegedly discloses antibody and immunogenic composition preparation and nucleic acid expression with a T7 RNA polymerase promoter. It also has been alleged that Halpern discloses expression of the nucleic acids of Halpern in recombinant mammalian host cells as well as recovery of the expressed protein.

Applicants traverse this rejection and assert that the claims, as amended herein, are not anticipated by Halpern. This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein. Applicants note

that the Examiner has included non-elected claims 83 and 84 in this rejection. Applicants suspect that this is a simple clerical error, but respectfully request clarification.

Claims 43 and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope". Applicants respectfully invite the Examiner's attention to Alignment 10 attached hereto which shows that the sequence of Halpern is not the same as the polypeptide sequence of SEQ ID NO:8 of the present invention. Therefore, since Halpern fails to teach Smith SEQ ID NO:8, Halpern fails anticipate each and every element of claims 43 and 53. Consequently, Applicants respectfully request withdrawal of this rejection.

#### **4. Whalen Does Not Teach SEQ ID NO:8**

Claims 39-47, 53-56, 82, and 85-86 have been rejected under 35 U.S.C. §102(b) as allegedly unpatentable over Whelan SM et al., April 26, 1993, Accession M81186 GI:144743 (hereinafter "Whalen"). Whalen allegedly discloses a nucleic acid which encodes the carboxy-terminal portion of the heavy chain of botulinum neurotoxin serotype B. The Examiner has alleged that the nucleic acid of Whalen would be capable of expression in an organism selected from the group consisting of gram negative bacteria, yeast, and a mammalian cell line.

Applicants traverse this rejection and assert that the claims, as amended herein, are not anticipated by Whalen. As a preliminary matter, Applicants request clarification of two issues related to this rejection. First, Applicants note that the Office Action dated November 7, 2002 indicated that Accession M81186 was published on May 28, 1992. Applicants respectfully invite the Examiner's attention to an enclosed printout of the Sequence Revision History that Applicants obtained from <http://www.ncbi.nlm.nih.gov/entrez/sutils/girevhist.cgi>, which indicates that the nucleotide and amino acid sequences assigned Accession M81186 were "first

seen at NCBI on Apr 26 1993 16:35". Therefore, Applicants respectfully request clarification of the basis for the Examiner's use of the May 28, 1992 date.

Second, the Examiner has stated "[t]he nucleic acid was cloned and found to encode a polypeptide of 623 amino acids of the H chain (see abstract)". Paper 11, Office Action dated November 11, 2002, p. 17, paragraph 23, lines 7-8. However, Applicants respectfully invite the Examiner's attention to the disclosure published by NCBI as Accession M81186 and note that there is no abstract and very little annotation of any kind. Moreover, the annotation that is present discloses an amino acid sequence of 1291 amino acids, not 623 amino acids.

Applicants, therefore, respectfully request clarification.

This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein.

Claims 43 and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope". Applicants respectfully invite the Examiner's attention to Alignments 11 and 12 attached hereto, which show that the sequence of Accession No. M81186 is not the same as the sequences of SEQ ID NOS:7 and 8 respectively of the present invention. Therefore, since Whalen fails to teach the instant SEQ ID NO:8, Whalen fails anticipate each and every element of claims 43 and 53. Applicants further contend that the nucleic acid of Whalen, with total AT content of 74.56% and an AT content over the aligned region of 76.45%, would be nonexpressible in yeast and poorly expressible or nonexpressible in gram negative bacteria and mammalian cell lines. *See e.g.* page 14, lines 20-22. Consequently, Applicants respectfully request withdrawal of this rejection.

## 5. Jung Does Not Teach SEQ ID NO:8

Claims 39-50, 53-56, 82, and 85-86 have been rejected under 35 U.S.C. §102(b) as allegedly unpatentable over Jung HH et al., 1992, *FEMS Microbiol Lett.* **91**:69-72 (hereinafter "Jung"). Jung allegedly discloses a nucleotide sequence that encodes a carboxy-terminal portion of the heavy chain of a botulinum neurotoxin serotype B. The Examiner alleges that the nucleic acid of Jung comprises a nucleotide sequence selected from SEQ ID NO:7 and would encode an amino acid sequence of SEQ ID NO:8.

Applicants traverse this rejection and assert that Jung fails to anticipate the instant invention. This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein.

Applicants respectfully invite the Examiner's attention to the title and the Summary of Jung, both of which clearly indicate that Jung relates to the **amino**-terminal end of the heavy chain of botulinum neurotoxin serotype B. Applicants claims relate to the **carboxy**-terminal end of the heavy chain of botulinum neurotoxin serotype B. Applicants further invite the Examiner's attention to Alignments 13 and 14 attached hereto, which show that Jung is not the same as SEQ ID NOS:7 and 8. Therefore, Jung clearly fails to teach a nucleic acid of Smith SEQ ID NO:7 that encodes an amino acid sequence of Smith SEQ ID NO:8.

Moreover, contrary to the Examiner's assertion that the sequence of Jung would naturally evidence an AT content of less than 60%-70%, the nucleic acid of Jung actually has an AT content of 75.87% over the region for which the nucleotide sequence is disclosed. Moreover, one of ordinary skill in the art would **not** expect the full-length sequence to deviate from this figure substantially, since it is well known to those of skill in the art that the native neurotoxin genes of *Clostridium botulinum* are known to have a **high** AT content. See e.g. page 14, lines 7-

11 and Whalen (full-length AT = 74.56%). Therefore, Jung neither expressly teaches nor inherently discloses SEQ ID NO:8 or a sequence which encodes it. Consequently, Applicants respectfully request withdrawal of this rejection.

#### **6. The '665 Patent Does Not Teach SEQ ID NO:8**

Claims 39-47 and 55-56 have been rejected under 35 U.S.C. §102(e) as allegedly unpatentable over U.S. Patent No. 5,919,665 to Williams et al. (hereinafter "the '665 patent"). The Examiner has alleged that a portion of SEQ ID NO:7 is 100% identical to a portion of SEQ ID NO:22, 25 or 27 of the '665 patent.

Applicants traverse this rejection and assert that the claims, as amended herein, are not anticipated by the '665 patent. This rejection will be moot as to claims 39-41 and 54 upon entry of the instant Amendment in view of the cancellation of these claims herein.

Claims 43, 48, and 53 each recite a "a nucleotide sequence encoding a polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope". Applicants respectfully invite the Examiner's attention to Alignments 15-20 attached hereto, which show that SEQ ID NOS:22, 25, and 27 of the '665 patent and the respective polypeptides encoded thereby, *i.e.* SEQ ID NOS:23, 26, and 28, are not the same as invention SEQ ID NOS:7 and 8 of the present invention. Therefore, since SEQ ID NOS: 22, 23, and 25-28 of the '665 patent fail to teach SEQ ID NO:8 of the present invention, the '665 patent fails anticipate each and every element of claims 43, 48, and 53. Consequently, Applicants respectfully request withdrawal of this rejection of these independent claims as well as the attendant dependent claims.

In conclusion, claims 42-51, 53, 55-56, 82, and 85-86 are drawn to statutory subject matter, recite language that complies with 35 U.S.C. §112, and are not anticipated by any

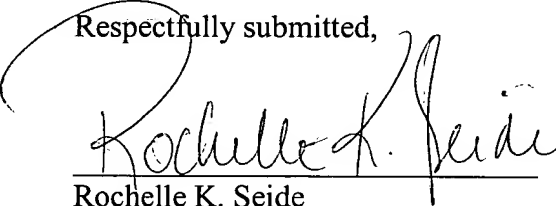
of the asserted documents. Therefore, Applicants believe this application is in condition for allowance and respectfully request issuance of a Notice of Allowance.

Applicants note that the Office Action dated November 7, 2002 included several sequence alignments. However, Applicants found it difficult to interpret these alignments due to the absence of meaningful labels and/or the poor quality of the photocopies provided. Therefore, should the Examiner continue to maintain any of the foregoing art rejections, Applicants respectfully request new alignments with clear labels identifying which invention sequence is aligned with which sequence of the asserted art.

Applicants request a one-month extension of time and enclose the fee required pursuant to 37 C.F.R. §1.17(a)(1). Applicants also enclose the fee required pursuant to 37 C.F.R. §1.17(p) and 1.97(c). Applicants do not believe that any additional fees are due with this submission. Nevertheless, the Commissioner is hereby authorized to charge any fees due with this submission not otherwise enclosed herewith to Deposit Account No. 02-4377. Please credit any overpayment of fees associated with this filing to the above-identified deposit account. A duplicate of this page is enclosed. A copy of the Notice to Comply is also enclosed.

March 7, 2003

Respectfully submitted,



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Enclosures



**VERSION WITH MARKINGS TO SHOW CHANGES MADE**

This marked-up version was prepared with DeltaView software (v2.7). In this section, added text is marked with double underlining. *e.g.* added text, and deleted text is marked by a single strikethrough, *e.g.* ~~deleted text~~.

**IN THE SPECIFICATION**

The paragraphs beginning at page 6, line 20 and ending at page 6, line 32 have been **amended** as follows:

~~It is an object of this~~The instant invention ~~to provide~~provides immunogenic peptides capable of eliciting protective immunity against botulinum neurotoxin of serotypes A-G.

~~It is another object of this~~The instant invention ~~to also provide~~provides vaccines capable of eliciting protective immunity against botulinum neurotoxin, where the vaccines do not act as neurotoxins themselves.

~~It is yet another object of this~~The instant invention ~~to further provide~~provides methods for preparing non-toxic peptides for use in vaccines against botulinum neurotoxin by growing recombinant organisms which express the peptides.

~~It is still another object of this~~The instant  
invention ~~tealso provide~~provides methods for fast and  
efficient purification of the non-toxic peptides from  
cultures of recombinant organisms.

These and other ~~objects~~aspects are ~~met~~illustrated  
by one or more of the following embodiments of the present  
invention.

The paragraphs beginning at page 9, line 20 and ending at page 11, line 12 have  
been **amended** as follows:

~~Figure 1 shows the~~Figures 1A and 1B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype A (SEQ ID NOS:1 ~~and the encoded amino acids~~  
~~sequence2~~).

~~Figure 2 shows the~~Figures 2A and 2B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype A (SEQ ID NOS:3 ~~and the encoded amino acids~~  
~~sequence4~~).

~~Figure 3 shows the~~Figures 3A and 3B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype A (SEQ ID NOS:5 and ~~the encoded amino acids~~  
~~sequence~~6).

~~Figure 4 shows the~~Figures 4A and 4B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype B (SEQ ID NOS:7 and ~~the encoded amino acids~~  
~~sequence~~8).

~~Figure 5 shows the~~Figures 5A and 5B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype C (SEQ ID NOS:9 and ~~the encoded amino acids~~  
~~sequence~~10).

~~Figure 6 shows the~~Figures 6A and 6B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of  
BoNT serotype D (SEQ ID NOS:11 and ~~the encoded amino acids~~  
~~sequence~~12).

~~Figure 7 shows the~~Figures 7A and 7B respectively  
show the nucleotide sequence and the encoded amino acid

sequence for a synthetic gene encoding the H<sub>c</sub> fragment of BoNT serotype E (SEQ ID NOS:13 and the ~~encoded amino acids sequence~~14).

Figure 8 shows the nucleotide sequence for a synthetic gene encoding the H<sub>c</sub> fragment of BoNT serotype E and the encoded amino ~~acids~~acid sequence (SEQ ID NOS:35 and 36).

~~Figure 9 shows the~~Figures 9A and 9B respectively  
show the nucleotide sequence and the encoded amino acid  
sequence for a synthetic gene encoding the H<sub>c</sub> fragment of BoNT serotype F (SEQ ID NOS:15 and the ~~encoded amino acids sequence~~16).

~~Figure 10 shows the~~Figures 10A and 10B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>c</sub> fragment of BoNT serotype G (SEQ ID NOS:17 and the ~~encoded amino acids sequence~~18).

~~Figure 11 shows the~~Figures 11A and 11B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub> fragment of BoNT serotype A (SEQ ID NOS:19 and the ~~encoded amino acids sequence~~20).

~~Figure 12 shows the~~Figures 12A and 12B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub>  
fragment of BoNT serotype B (SEQ ID NOS:21 and ~~the encoded~~  
~~amino acids sequence~~22).

~~Figure 13 shows the~~Figures 13A and 13B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub>  
fragment of BoNT serotype C (SEQ ID NOS:23 and ~~the encoded~~  
~~amino acids sequence~~24).

~~Figure 14 shows the~~Figures 14A and 14B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub>  
fragment of BoNT serotype D (SEQ ID NOS:25 and ~~the encoded~~  
~~amino acids sequence~~26).

~~Figure 15 shows the~~Figures 15A and 15B  
respectively show the nucleotide sequence and the encoded  
amino acid sequence for a synthetic gene encoding the H<sub>N</sub>  
fragment of BoNT serotype E (SEQ ID NOS:27 and ~~the encoded~~  
~~amino acids sequence~~28).

~~Figure 16 shows the~~Figures 16A and 16B  
respectively show the nucleotide sequence and the encoded

amino acid sequence for a synthetic gene encoding the H<sub>N</sub> fragment of BoNT serotype F (SEQ ID NOS:29 and ~~the encoded amino acids sequence~~30).

~~Figure 17 shows the~~Figures 17A and 17B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H<sub>N</sub> fragment of BoNT serotype G (SEQ ID NOS:31 and ~~the encoded amino acids sequence~~32).

~~Figure 18 shows the~~Figures 18A and 18B respectively show the nucleotide sequence and the encoded amino acid sequence for a synthetic gene encoding the H<sub>C</sub> fragment of BoNT serotype F (SEQ ID NOS:33 and ~~the encoded amino acids sequence~~34).

Figures 19A, 19B, and 19C. Figure 19A shows ~~(A)the~~ AT base content of a putative fragment C region in native *C. botulinum* DNA. ~~(Figure 19B) Reduction at~~ shows the reduced AT content after the first design (rBoNTF(Hc)1) of the synthetic gene. ~~(Figure 19C)~~ shows the AT content of the final gene design (rBoNTF(Hc)2) used to express recombinant rBoNTF(Hc) in *P. pastoris*.

Figures 20A and 20B. Figure 20A shows ~~(A)an~~ SDS-PAGE gel and ~~(Figure 20B)~~ shows a Western blot of samples

at various steps along the rBoNTF(Hc) purification. Lanes from both figures are identical except lane 1, where SDS-PAGE shows Novex mark 12 wide-range molecular weight markers and Western blot shows Novex See Blue prestained molecular weight markers. Lane 2 is the cell lysate, lane 3 is the cell extract, lane 4 is the cell extract after dialysis, lane 5 is pool of rBoNTF(Hc) positive fractions after Mono S column chromatography, and lane 6 is pool of rBoNTF(Hc)-positive fractions after hydrophobic interaction chromatography.

~~Figure~~Figures 21A and 21B show purification of rBoNTF(Hc) by sequential chromatography. ~~(Figure 21A)~~ shows Mono S cation exchange chromatography of extract from *P. pastoris*. Proteins were eluted with increasing NaCl gradient. Fractions positive for rBoNTF(Hc) by Western analysis were pooled individually and subjected to hydrophobic interaction chromatography (the results of which are shown in Figure 21B) and proteins were eluted with a decreasing ammonium sulfate gradient. In both panels, protein monitored by A280nm is recorded on the left axis and elution conditions are recorded on the right axis, with the gradient trace laid over the chromatogram.

The paragraph beginning at page 12, line 7 and ending at page 12, line 14 has been **amended** as follows:

Kozaki et al. (in "Antibodies against Botulism Neurotoxin", L.L. Simpson, ed., 1989, Academic Press, New York) suggested that a protective epitope might be present in the 50 kDa carboxyl terminus (HC) region of the protein. Thompson et al. (1990, *Eur. J. Biochem.* **189**:73-81) deduced the amino acid sequence for the serotype A botulinum toxin. DasGupta et al. (1990, *Biochemie*, **72**:661-664) identified the "nick" site for post-translational cleavage of the expressed toxin polypeptide, from which the sequence of the heavy chain can be deduced as follows ~~(see~~SEQ ID NO:41. See also Krieglstein, et al., 1994, *J. Protein Chem.*, **13**:49-57)~~57.~~

The paragraph beginning at page 13, line 1 and ending at page 13, line 6 has been **amended** as follows:

Whelan et al. (*Appl. Environ. Microbiol.* **58**:2345-2354, 1992) have deduced the amino acid sequence for the serotype B botulinum toxin. Schmidt, et al. (1985, *Arch. Biochem. Biophys.*, **238**:544-548) provided N-terminal sequence information for the heavy chain resulting ~~from~~from



post-translational cleavage of the expressed toxin polypeptide, and the sequence of the heavy chain can be deduced from this information as ~~follows~~SEQ ID NO:42.

The paragraph beginning at page 36, line 17 and ending at page 36, line 17 has been **amended** as follows:

The sequence of the C fragment of the A chain was deduced as+ SEQ ID NO:38.

The paragraph beginning at page 36, line 32 and ending at page 36, line 32 has been **amended** as follows:

The sequence for the synthetic gene is ~~found~~  
~~below~~+SEQ ID NO:37.

The paragraph beginning at page 38, line 6 and ending at page 38, line 7 has been **amended** as follows:

The C fragment for botulism toxin serotype B of Whelan was studied and the portion of the protein having the sequence of SEQ ID NO:40 was defined as the C fragment.

The paragraph beginning at page 38, line 18 and ending at page 38, line 25 has been **amended** as follows:

The synthetic gene for expression in *E. coli* was produced in the manner described for synthesis of the gene for the C fragment of the A strand, namely, using a large number of oligomers of approximately 60-65 bases corresponding to the sequences of the + and - strands with overlaps of 7 bases. The oligomers were allowed to anneal and were ligated to form subunits of 250-300 base pairs each. Each subunit had been designed to have restriction sites at their termini which allowed them to be assembled in the right order to form the complete gene. ~~the~~The synthetic gene ~~for~~ encoding the eC fragment of the B toxin ~~was as follows~~is SEQ ID NO:39.

IN THE CLAIMS

Claims 42-49, 53, 55, 82, and 85-86 have been **amended** as follows:

42. (AMENDED) The nucleic acid of claim ~~39~~, 43, wherein said ~~nucleic acid comprises a nucleic acid~~nucleotide sequence ~~selected from the group consisting of~~is SEQ ID No. ~~7~~, SEQ ID No. ~~9~~, SEQ ID No. ~~11~~, SEQ ID No. ~~13~~, SEQ ID No. ~~15~~, and SEQ ID No. ~~17~~.NO:7.
43. (AMENDED) A nucleic acid ~~comprising~~having a nucleotide sequence ~~which encodes~~encoding a polypeptide ~~having an~~comprising the amino acid sequence ~~selected from the group consisting of~~ SEQ ID No. ~~NO:8~~, SEQ ID No. said amino acid sequence comprising at least one immunogenic epitope. ~~10~~, SEQ ID No. ~~12~~, SEQ ID No. ~~14~~, SEQ ID No. ~~16~~, and SEQ ID No. ~~18~~.
44. (AMENDED) The nucleic acid of claim ~~39~~, 43, wherein said nucleic acid is ~~an~~syntheticisolated nucleic acid.
45. (AMENDED) The nucleic acid of claim ~~39~~, wherein said ~~nucleic acid is operably linked to~~43 further comprising an expression control ~~sequence~~sequence operably linked to said nucleotide sequence.

46. (AMENDED) The nucleic acid of claim ~~39,45,~~ wherein said expression control ~~sequences~~sequence ~~comprise~~comprises a promoter.
47. (AMENDED) The nucleic acid of claim ~~39,45,~~ wherein said expression control ~~sequences~~sequence ~~comprise~~comprises an enhancer.
48. (AMENDED) A method of preparing a polypeptide comprising ~~the~~a carboxy-terminal portion of the heavy chain of a botulinum neurotoxin ~~serotype selected from the group consisting of serotype B comprising at least one immunogenic epitope, serotype C<sub>1</sub>, serotype D, serotype E, serotype F, and serotype G, said method comprising:~~
- ~~transfecting an organism~~a cell with ~~the~~a nucleic acid having a nucleotide sequence encoding a polypeptide having the amino acid sequence of claim 39, SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope; and
- culturing the transfected ~~organism~~cell under conditions wherein the ~~carboxy terminal portion of the heavy chain of a botulinum neurotoxin serotype~~nucleic acid is expressed,

wherein the ~~organism~~cell is selected from the group consisting of a gram negative bacteria, a yeast, and a mammalian cell~~line~~.

49. (AMENDED) The method of claim 48, further comprising recovering ~~insoluble protein from~~ said transfected ~~organism~~cell at least one insoluble polypeptide having the amino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope.

53. (AMENDED) A method of preparing ~~thean~~immunogenic composition comprising a polypeptide comprising the amino acid sequence of claim 52, SEQ ID NO:8, said methodamino acid sequence comprising at least one immunogenic epitope, comprising :

culturing a ~~recombinant host organism~~cell  
transfected with an expression vector comprising a nucleic acid comprising a nucleotide sequence encoding, in an expressable form, a polypeptide comprising the carboxy terminal portionamino acid sequence of SEQ ID NO:8, said amino acid sequence comprising at least one immunogenic epitope under conditions wherein the heavy chain of a botulinum

~~neurotoxin serotype.~~nucleic acid is expressed;

and

recovering from said transfected cell at least one

insoluble polypeptide comprising the amino acid

sequence of SEQ ID NO:8, said amino acid sequence

comprising at least one immunogenic epitope,

wherein the cell is selected from the group consisting  
of a gram negative bacteria, a yeast, and a mammalian  
cell.

55. (AMENDED) The nucleic acid of claim ~~39,43~~, wherein the A+TAT content is less than about 70% of the total base composition.
56. (AMENDED) The nucleic acid of claim 55, wherein the A+TAT content is less than about 60% of the total base composition.
82. (TWICE AMENDED) A recombinant host cell comprising the nucleic acid of claim ~~39,45~~.
85. (AMENDED) The recombinant host cell of claim 82, wherein said ~~protein~~polypeptide is at least 0.75% (w/w) of the total cellular protein.

86. (AMENDED) The recombinant host cell of claim 85,  
wherein said ~~protein~~polypeptide is at least 20% (w/w)  
of the total cellular protein.

IN THE SEQUENCE LISTING

The following alignments show the changes made to the indicated sequences and the support for these changes based on other sequences in the application. In this section, a summary of changes appears just before each alignment and changes are highlighted in the alignments. (SI# = SEQ ID NO; Ac# M81186 = Genbank accession number M81186, a copy of which is attached.)

Alignment 1

SEQ ID NO:41 (appearing on page 12 in the specification as filed) has been amended as follows:

- At position 717 of paragraph 1.8, Y has been inserted.
- At position 822 of paragraph 1.10, O→Q.

Paragraph 1.1														
	1	15	16	30	31	45	46	60	61	75	76	90		
As filed	ALNDLCIKVNNWDLF	FSPSEDNFTNDLNKG	EEITS	SDTNIEAAEEN	ISLDLIQYYLTFNF	DN	EPENIS	IE	NLSSD	IIGQLE	LMPN	IERFP	90	
Amended	ALNDLCIKVNNWDLF	FSPSEDNFTNDLNKG	EEITS	SDTNIEAAEEN	ISLDLIQYYLTFNF	DN	EPENIS	IE	NLSSD	IIGQLE	LMPN	IERFP	90	
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Paragraph 1.2														
	91	105	106	120	121	135	136	150	151	165	166	180		
As filed	NGKKYELDKYTMFHY	LRAQEF	EHGKSRIAL	TNSVNE	ALLNPSRVY	TFSSDY	VKKVNKAT	EAAMFL	GWVEQLVYD	FTDET	SEVSTTDKIA	180		
Amended	NGKKYELDKYTMFHY	LRAQEF	EHGKSRIAL	TNSVNE	ALLNPSRVY	TFSSDY	VKKVNKAT	EAAMFL	GWVEQLVYD	FTDET	SEVSTTDKIA	180		
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0		
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0		
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0		
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0		
Paragraph 1.3														
	181	195	196	210	211	225	226	240	241	255	256	270		
As filed	DITIIIPYIGPALNI	GMLYKDD	FVGALIFS	GAVILLE	FIPEIAIP	VLGTFAL	VS	YIANKV	LTVQT	IDNAL	SKRNE	KWDEVY	KYIVTNWLA	270
Amended	DITIIIPYIGPALNI	GMLYKDD	FVGALIFS	GAVILLE	FIPEIAIP	VLGTFAL	VS	YIANKV	LTVQT	IDNAL	SKRNE	KWDEVY	KYIVTNWLA	270
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Paragraph 1.4														
	271	285	286	300	301	315	316	330	331	345	346	360		
As filed	KVNTQIDLIRKKMKE	ALENQAE	ATKAIINY	QYNQY	TEEEKNNINF	NIDDLSS	KLNESINK	AMININK	FLNQCSVS	YLMNSM	IPYGVKRL	E	360	
Amended	KVNTQIDLIRKKMKE	ALENQAE	ATKAIINY	QYNQY	TEEEKNNINF	NIDDLSS	KLNESINK	AMININK	FLNQCSVS	YLMNSM	IPYGVKRL	E	360	
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0	



## Paragraph 1.5

	361	375	376	390	391	405	406	420	421	435	436	450
As filed	DFDASLKDALLKYIR	DNYGTLIGQVDRLKD	KVNNTLSTDIPIFQLS	KYVDNQRLSTFTTEY	IKNIINTSILNRLYE	SNHLIDLSRYASKIN						450
Amended	DFDASLKDALLKYIR	DNYGTLIGQVDRLKD	KVNNTLSTDIPIFQLS	KYVDNQRLSTFTTEY	IKNIINTSILNRLYE	SNHLIDLSRYASKIN						450
P.36 SI#38	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	18
Fig.3 SI#6	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	38
Fig.2 SI#4	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	37
Fig.1 SI#2	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	40

## Paragraph 1.6

	451	465	466	480	481	495	496	510	511	525	526	540
As filed	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNSISLN	NEYTIINCMENNSGW	KVSLNYGEIIWTLQD						540
Amended	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNSISLN	NEYTIINCMENNSGW	KVSLNYGEIIWTLQD						540
P.36 SI#38	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNSISLN	NEYTIINCMENNSGW	KVSLNYGEIIWTLQD						108
Fig.3 SI#6	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNSISLN	NEYTIINCMENNSGW	KVSLNYGEIIWTLQD						128
Fig.2 SI#4	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNSISLN	NEYTIINCMENNSGW	KVSLNYGEIIWTLQD						127
Fig.1 SI#2	IGSKVNFDPIDKNQI	QLFNLESSKIEVILK	NAIVNSMYENFSTS	FWIRIPKYFNSISLN	NEYTIINCMENNSGW	KVSLNYGEIIWTLQD						130

## Paragraph 1.7

	541	555	556	570	571	585	586	600	601	615	616	630
As filed	TQEIKQRVVFYKYSQM	INISDYINRWIFVTI	TNNRLNNSKIYTING	RLIDQKPISNLGNH	ASNNIMFKLDGCRDT	HRWIWIKYFNLFDKE						630
Amended	TQEIKQRVVFYKYSQM	INISDYINRWIFVTI	TNNRLNNSKIYTING	RLIDQKPISNLGNH	ASNNIMFKLDGCRDT	HRWIWIKYFNLFDKE						630
P.36 SI#38	TQEIKQRVVFYKYSQM	INISDYINRWIFVTI	TNNRLNNSKIYIN-G	RLIDQKPISNLGNH	ASNNIMFKLDGCRDT	HRWIWIKYFNLFDKE						197
Fig.3 SI#6	TQEIKQRVVFYKYSQM	INISDYINRWIFVTI	TNNRLNNSKIYIN-G	RLIDQKPISNLGNH	ASNNIMFKLDGCRDT	HRWIWIKYFNLFDKE						217
Fig.2 SI#4	TQEIKQRVVFYKYSQM	INISDYINRWIFVTI	TNNRLNNSKIYIN-G	RLIDQKPISNLGNH	ASNNIMFKLDGCRDT	HRWIWIKYFNLFDKE						216
Fig.1 SI#2	TQEIKQRVVFYKYSQM	INISDYINRWIFVTI	TNNRLNNSKIYIN-G	RLIDQKPISNLGNH	ASNNIMFKLDGCRDT	HRWIWIKYFNLFDKE						219

## Paragraph 1.8

	631	645	646	660	661	675	676	690	691	705	706	720
As filed	LNEKEIKDLYDNQSN	SGILKDFWGDYLYQD	KPYYMILLYDPNKYV	DVNNVGIRGYMYLKG	PRGSVMTTNIYLNSS	LYRGTKFIIKKYASG						719
Amended	LNEKEIKDLYDNQSN	SGILKDFWGDYLYQD	KPYYMILLYDPNKYV	DVNNVGIRGYMYLKG	PRGSVMTTNIYLNSS	LYRGTKFIIKKYASG						719
P.36 SI#38	LNEKEIKDLYDNQSN	SGILKDFWGDYLYQD	KPYYMILLYDPNKYV	DVNNVGIRGYMYLKG	PRGSVMTTNIYLNSS	LYRGTKFIIKKYASG						287
Fig.3 SI#6	LNEKEIKDLYDNQSN	SGILKDFWGDYLYQD	KPYYMILLYDPNKYV	DVNNVGIRGYMYLKG	PRGSVMTTNIYLNSS	LYRGTKFIIKKYASG						307
Fig.2 SI#4	LNEKEIKDLYDNQSN	SGILKDFWGDYLYQD	KPYYMILLYDPNKYV	DVNNVGIRGYMYLKG	PRGSVMTTNIYLNSS	LYRGTKFIIKKYASG						306
Fig.1 SI#2	LNEKEIKDLYDNQSN	SGILKDFWGDYLYQD	KPYYMILLYDPNKYV	DVNNVGIRGYMYLKG	PRGSVMTTNIYLNSS	LYRGTKFIIKKYASG						309

## Paragraph 1.9

	721	735	736	750	751	765	766	780	781	795	796	810
As filed	NKDNIVRNNDRVYIN	VVVKNEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHQFNNI						809
Amended	NKDNIVRNNDRVYIN	VVVKNEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHQFNNI						809
P.36 SI#38	NKDNIVRNNDRVYIN	VVVKNEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHQFNNI						377
Fig.3 SI#6	NKDNIVRNNDRVYIN	VVVKNEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHQFNNI						397
Fig.2 SI#4	NKDNIVRNNDRVYIN	VVVKNEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHQFNNI						396
Fig.1 SI#2	NKDNIVRNNDRVYIN	VVVKNEYRLATNAS	QAGVEKILSALEIPD	VGNLSQVVVMKSKND	QGITNKCKMNLQDNN	GNDIGFIGFHQFNNI						399

## Paragraph 1.10

	811	825	826	840	841	855	856	870	871	885	886	900
As filed	AKLVASNWNRYQTER	SSRTLGCSEWEIFVD	DGWGERPL									
Amended	AKLVASNWNRYQTER	SSRTLGCSEWEIFVD	DGWGERPL									
P.36 SI#38	AKLVASNWNRYQIER	SSRTLGCSEWEIFVD	DGWGERPL									
Fig.3 SI#6	AKLVASNWNRYQIER	SSRTLGCSEWEIFVD	DGWGERPL									
Fig.2 SI#4	AKLVASNWNRYQIER	SSRTLGCSEWEIFVD	DGWGERPL									
Fig.1 SI#2	AKLVASNWNRYQIER	SSRTLGCSEWEIFVD	DGWGERPL									

**Alignment 2**

SEQ ID NO:42 (appearing on page 13 in the specification as filed) has been amended as

follows:

- At position 911 of paragraph 2.11, T→V.
- At position 969 of paragraph 2.11, N has been inserted.
- At position 1110 of paragraph 2.13, T has been deleted.
- At position 1193 of paragraph 2.14, K has been inserted.
- At position 1254 of paragraph 2.14, V→Y.
- At position 1257 of paragraph 2.14, V→Y.
- At position 1262 of paragraph 2.15, D→K.
- At position 1269 of paragraph 2.15, K has been inserted.

Paragraph 2.1

1	15	16	30	31	45	46	60	61	75	76	90	
As filed	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Amended	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Ac# M81186	MPVTINNPNYNDPID	NNNIIMMEPPFARGT	GRYYKAFKITDRIWI	IPERYTFGYKPEDFN	KSSGIFNRDVCCEYYD	PDYLTNDKKNIFLQ						90

Paragraph 2.2

91	105	106	120	121	135	136	150	151	165	166	180	
As filed	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Amended	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Ac# M81186	TMIKLFNRIKSKPLG	EKLLEMIINGIPYLG	DRRVPLEEFNTNIAS	VTVNKLISNPGEVER	KKGIFANLIIFGPGP	VLNENETIDIGIQNH						180

Paragraph 2.3

181	195	196	210	211	225	226	240	241	255	256	270	
As filed	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Amended	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Ac# M81186	FASREGFGGIMQMKF	CPEYVSVPNNVQENK	GASIFNRRGYFSDPA	LILMHელიHVLHGLY	GIKVDDLPIVPNEKK	FFMQSTDAIQAEELY						270

Paragraph 2.4

271	285	286	300	301	315	316	330	331	345	346	360	
As filed	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Amended	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Ac# M81186	TFGGQDPSIITPSTD	KSIYDKVLQNFRTIV	DRLNKVLVCISDPNI	NINIYKNKFKDKYKF	VEDSEGKYSIDVESF	DKLYKSLMFGPTETN						360

Paragraph 2.5

361	375	376	390	391	405	406	420	421	435	436	450	
As filed	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	9
Amended	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	9
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Ac# M81186	IAENYKIKTRASYFS	DSLPPVKIKNLLDNE	IYTIEEGFNISDKDM	EKEYRGQNKAINKQA	YEEISKEHLAVYKIQ	MCKSVKAPGICIDVD						450

## Paragraph 2.6

	451	465	466	480	481	495	496	510	511	525	526	540	
As filed	NEDLFFIADKNSFSD	DLSKNERIEYNTQSN	YIENDFPINELILDT	DLISKIELPSENTES	LTDFNVDPVYEQP	AIKKIFTDENTIFQY							99
Amended	NEDLFFIADKNSFSD	DLSKNERIEYNTQSN	YIENDFPINELILDT	DLISKIELPSENTES	LTDFNVDPVYEQP	AIKKIFTDENTIFQY							99
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Ac# M81186	NEDLFFIADKNSFSD	DLSKNERIEYNTQSN	YIENDFPINELILDT	DLISKIELPSENTES	LTDFNVDPVYEQP	AIKKIFTDENTIFQY							540

## Paragraph 2.7

	541	555	556	570	571	585	586	600	601	615	616	630	
As filed	LYSQTFPLDIRDISL	TSSFDDALLFSNKVY	SFFSMDYIKTANKVV	EAGLFAGWVKQIVND	FVIEANKSNTMDKIA	DISLIVPYIGLALNV							189
Amended	LYSQTFPLDIRDISL	TSSFDDALLFSNKVY	SFFSMDYIKTANKVV	EAGLFAGWVKQIVND	FVIEANKSNTMDKIA	DISLIVPYIGLALNV							189
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Ac# M81186	LYSQTFPLDIRDISL	TSSFDDALLFSNKVY	SFFSMDYIKTANKVV	EAGLFAGWVKQIVND	FVIEANKSNTMDKIA	DISLIVPYIGLALNV							630

## Paragraph 2.8

	631	645	646	660	661	675	676	690	691	705	706	720	
As filed	GNETAKGNFENAFEI	AGASILLEFIPELLI	PVVGAFLLSEYIDNK	NKIIKTIDNALTKRN	EKWSMDYGLIVAQWL	STVNTQFYTIKEGMY							279
Amended	GNETAKGNFENAFEI	AGASILLEFIPELLI	PVVGAFLLSEYIDNK	NKIIKTIDNALTKRN	EKWSMDYGLIVAQWL	STVNTQFYTIKEGMY							279
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Ac# M81186	GNETAKGNFENAFEI	AGASILLEFIPELLI	PVVGAFLLSEYIDNK	NKIIKTIDNALTKRN	EKWSMDYGLIVAQWL	STVNTQFYTIKEGMY							720

## Paragraph 2.9

	721	735	736	750	751	765	766	780	781	795	796	810	
As filed	KALNYQAQALEEIIK	YRYNIYSEKEKSNIN	IDFNDINSKLNIGIN	QAIDNINNFINCGSV	SYLMKKMIPLAVEKL	LDPDNTLKKNLNLYI							369
Amended	KALNYQAQALEEIIK	YRYNIYSEKEKSNIN	IDFNDINSKLNIGIN	QAIDNINNFINCGSV	SYLMKKMIPLAVEKL	LDPDNTLKKNLNLYI							369
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	0
Ac# M81186	KALNYQAQALEEIIK	YRYNIYSEKEKSNIN	IDFNDINSKLNIGIN	QAIDNINNFINCGSV	SYLMKKMIPLAVEKL	LDPDNTLKKNLNLYI							810

## Paragraph 2.10

	811	825	826	840	841	855	856	870	871	885	886	900	
As filed	DENKLYLIGSAEYK	SKVNKYLKTIMPFDL	SIYTNDTILIEFMNK	YNSEILNNIILNLRY	KDNNLIDLSGYGAKV	EVYDGVELNDKNQFK							459
Amended	DENKLYLIGSAEYK	SKVNKYLKTIMPFDL	SIYTNDTILIEFMNK	YNSEILNNIILNLRY	KDNNLIDLSGYGAKV	EVYDGVELNDKNQFK							459
Fig 4 SI#8	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	-----	49
Ac# M81186	DENKLYLIGSAEYK	SKVNKYLKTIMPFDL	SIYTNDTILIEFMNK	YNSEILNNIILNLRY	KDNNLIDLSGYGAKV	EVYDGVELNDKNQFK							900

## Paragraph 2.11

	901	915	916	930	931	945	946	960	961	975	976	990	
As filed	LTSSANSKIRVTQNG	NIIFNSVFLDFSVSF	WIRIPKYKNDGIQNY	IHNEYTIINCMKNNS	GWKISIRGRIIWTL	IDINGKTKSVFFEYN							548
Amended	LTSSANSKIRVTQNG	NIIFNSVFLDFSVSF	WIRIPKYKNDGIQNY	IHNEYTIINCMKNNS	GWKISIRGRIIWTL	IDINGKTKSVFFEYN							549
Fig 4 SI#8	LTSSANSKIRVTQNG	NIIFNSVFLDFSVSF	WIRIPKYKNDGIQNY	IHNEYTIINCMKNNS	GWKISIRGRIIWTL	IDINGKTKSVFFEYN							139
Ac# M81186	LTSSANSKIRVTQNG	NIIFNSVFLDFSVSF	WIRIPKYKNDGIQNY	IHNEYTIINCMKNNS	GWKISIRGRIIWTL	IDINGKTKSVFFEYN							990

## Paragraph 2.12

	991	1005	1006	1020	1021	1035	1036	1050	1051	1065	1066	1080	
As filed	IREDISSEYINRWFFV	TITNNLNNAKIYING	KLESNTDIKDIREVI	ANGEIIFKLDGDIDR	TQFIWMKYFSIFNTE	LSQSNIEERYKIQSY							638
Amended	IREDISSEYINRWFFV	TITNNLNNAKIYING	KLESNTDIKDIREVI	ANGEIIFKLDGDIDR	TQFIWMKYFSIFNTE	LSQSNIEERYKIQSY							639
Fig 4 SI#8	IREDISSEYINRWFFV	TITNNLNNAKIYING	KLESNTDIKDIREVI	ANGEIIFKLDGDIDR	TQFIWMKYFSIFNTE	LSQSNIEERYKIQSY							229
Ac# M81186	IREDISSEYINRWFFV	TITNNLNNAKIYING	KLESNTDIKDIREVI	ANGEIIFKLDGDIDR	TQFIWMKYFSIFNTE	LSQSNIEERYKIQSY							1080

## Paragraph 2.13

	1081	1095	1096	1110	1111	1125	1126	1140	1141	1155	1156	1170	
As filed	SEYLKDFWGNPLMYN	KEYYMFNAGNKNSYT	IKLKKDSPVGEILTR	SKYNQNSKYINYRDL	YIGKEFIIRKKSNSQ	SINDDIVRKEDYIYL							728
Amended	SEYLKDFWGNPLMYN	KEYYMFNAGNKNSYT	IKLKKDSPVGEILTR	SKYNQNSKYINYRDL	YIGKEFIIRKKSNSQ	SINDDIVRKEDYIYL							728
Fig 4 SI#8	SEYLKDFWGNPLMYN	KEYYMFNAGNKNSYT	IKLKKDSPVGEILTR	SKYNQNSKYINYRDL	YIGKEFIIRKKSNSQ	SINDDIVRKEDYIYL							318
Ac# M81186	SEYLKDFWGNPLMYN	KEYYMFNAGNKNSYT	IKLKKDSPVGEILTR	SKYNQNSKYINYRDL	YIGKEFIIRKKSNSQ	SINDDIVRKEDYIYL							1169

## Paragraph 2.14

	1171	1185	1186	1200	1201	1215	1216	1230	1231	1245	1246	1260	
As filed	DFFNLNQEWVRVYTYK	YFKKEEE-LFLAPIS	DSDEFYNTIQIKEYD	EQPTYSCQLLFKKDE	ESTDEIGLIGIHRFY	ESGIVFEEYKDYFCI							817
Amended	DFFNLNQEWVRVYTYK	YFKKEEE-LFLAPIS	DSDEFYNTIQIKEYD	EQPTYSCQLLFKKDE	ESTDEIGLIGIHRFY	ESGIVFEEYKDYFCI							818
Fig 4 SI#8	DFFNLNQEWVRVYTYK	YFKKEEE-LFLAPIS	DSDEFYNTIQIKEYD	EQPTYSCQLLFKKDE	ESTDEIGLIGIHRFY	ESGIVFEEYKDYFCI							408
Ac# M81186	DFFNLNQEWVRVYTYK	YFKKEEE-LFLAPIS	DSDEFYNTIQIKEYD	EQPTYSCQLLFKKDE	ESTDEIGLIGIHRFY	ESGIVFEEYKDYFCI							1259

## Paragraph 2.15

	1261	1275	1276	1290	1291	1305	1306	1320	1321	1335	1336	1350	
As filed	SKWYLKEVKKRPYNL	KLGCNWQFIPKDEGW	TE	848									
Amended	SKWYLKEVKKRPYNL	KLGCNWQFIPKDEGW	TE	850									
Fig 4 SI#8	SKWYLKEVKKRPYNL	KLGCNWQFIPKDEGW	TE	440									
Ac# M81186	SKWYLKEVKKRPYNL	KLGCNWQFIPKDEGW	TE	1291									

**Alignment 3**

SEQ ID NO:37 (appearing on page 37 in the specification as filed) has been amended as

follows:

- At position 147 of paragraph 3.2, C→G.
- At position 287 of paragraph 3.4, G is inserted.
- At position 535 of paragraph 3.6, G is inserted.
- At position 583 of paragraph 3.7, C is inserted.
- At position 956 of paragraph 3.11, D→C.
- At positions 957-959 of paragraph 3.11, GTT is inserted.

*Not identical  
all synthetic*

Paragraph 3.1

1	15	16	30	31	45	46	60	61	75	76	90	
As filed	---	CTCGAGCCATGG	CTCGTCTGCTGTCTA	CCTTCACTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT					87
Amended	---	CTCGAGCCATGG	CTCGTCTGCTGTCTA	CCTTCACTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT					87
Fig.1 SI#1	GAATTCGAAACGATG	CGT--	CTGCTGTCTA	CCTTCACTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT					88
Fig.3 SI#5	GAATTCGAAACGATG	G-----	CCTCTA	CCTTCACTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT					82
Fig.2 SI#3	GAATTCGAAACGATG	T-----	CTA	CCTTCACTGAATACA	TCAAGAACATCATCA	ATACCTCCATCCTGA	ACCTGCGCTACGAAT					79

Paragraph 3.2

91	105	106	120	121	135	136	150	151	165	166	180	
As filed	CCAATCACCTGATCG	ACCTGTCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAAGTTA	ACTTCGATCCGATCG	ACAAGAATCAGATCC						177
Amended	CCAATCACCTGATCG	ACCTGTCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAAGTTA	ACTTCGATCCGATCG	ACAAGAATCAGATCC						177
Fig.1 SI#1	CCAATCACCTGATCG	ACCTGTCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAAGTTA	ACTTCGATCCGATCG	ACAAGAATCAGATCC						178
Fig.3 SI#5	CCAATCACCTGATCG	ACCTGTCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAAGTTA	ACTTCGATCCGATCG	ACAAGAATCAGATCC						172
Fig.2 SI#3	CCAATCACCTGATCG	ACCTGTCTCGCTACG	CTTCCAAAATCAACA	TCGGTTCTAAAGTTA	ACTTCGATCCGATCG	ACAAGAATCAGATCC						169

Paragraph 3.3

181	195	196	210	211	225	226	240	241	255	256	270	
As filed	AGCTGTTCAATCTGG	AATCTTCCAAAATCG	AAGTTATCCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT						267
Amended	AGCTGTTCAATCTGG	AATCTTCCAAAATCG	AAGTTATCCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT						267
Fig.1 SI#1	AGCTGTTCAATCTGG	AATCTTCCAAAATCG	AAGTTATCCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT						268
Fig.3 SI#5	AGCTGTTCAATCTGG	AATCTTCCAAAATCG	AAGTTATCCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT						262
Fig.2 SI#3	AGCTGTTCAATCTGG	AATCTTCCAAAATCG	AAGTTATCCTGAAGA	ATGCTATCGTATACA	ACTCTATGTACGAAA	ACTTCTCCACCTCCT						259

Paragraph 3.4

271	285	286	300	301	315	316	330	331	345	346	360	
As filed	TCTGGATCCGTATCC	C-AAATACTTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTGCATGGAAA	ACAATTCTGGTTGGA						356
Amended	TCTGGATCCGTATCC	CGAAATACTTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTGCATGGAAA	ACAATTCTGGTTGGA						357
Fig.1 SI#1	TCTGGATCCGTATCC	CGAAATACTTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTGCATGGAAA	ACAATTCTGGTTGGA						358
Fig.3 SI#5	TCTGGATCCGTATCC	CGAAATACTTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTGCATGGAAA	ACAATTCTGGTTGGA						352
Fig.2 SI#3	TCTGGATCCGTATCC	CGAAATACTTCAACT	CCATCTCTCTGAACA	ATGAATACACCATCA	TCAACTGCATGGAAA	ACAATTCTGGTTGGA						349

Paragraph 3.5

361	375	376	390	391	405	406	420	421	435	436	450	
As filed	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA						446
Amended	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA						447
Fig.1 SI#1	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA						448
Fig.3 SI#5	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA						442
Fig.2 SI#3	AAGTATCTCTGAACT	ACGGTGAAATCATCT	GGACTCTGCAGGACA	CTCAGGAAATCAAAC	AGCGTGTGTATTCA	AATACTCTCAGATGA						439

## Paragraph 3.6

	451	465	466	480	481	495	496	510	511	525	526	540	
As filed	TCAACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGTCTGA	ATAAATCCAAAAATCT	ACATCAACG-CCGTC							535
Amended	TCAACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGTCTGA	ATAAATCCAAAAATCT	ACATCAACGCGCGTC							537
Fig.1 SI#1	TCAACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGTCTGA	ATAAATCCAAAAATCT	ACATCAACGCGCGTC							538
Fig.3 SI#5	TCAACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGTCTGA	ATAAATCCAAAAATCT	ACATCAACGCGCGTC							532
Fig.2 SI#3	TCAACATCTCTGACT	ACATCAATCGCTGGA	TCTTCGTTACCATCA	CCAACAATCGTCTGA	ATAAATCCAAAAATCT	ACATCAACGCGCGTC							529

## Paragraph 3.7

	541	555	556	570	571	585	586	600	601	615	616	630	
As filed	TGATCGACCAGAAAC	CGATCTCCAATCTGG	GTAACATCCACG-TT	CTAATAACATCATGT	TCAAACCTGGACGGTT	GTCGTGACACTCACC							624
Amended	TGATCGACCAGAAAC	CGATCTCCAATCTGG	GTAACATCCACGCTT	CTAATAACATCATGT	TCAAACCTGGACGGTT	GTCGTGACACTCACC							627
Fig.1 SI#1	TGATCGACCAGAAAC	CGATCTCCAATCTGG	GTAACATCCACGCTT	CTAATAACATCATGT	TCAAACCTGGACGGTT	GTCGTGACACTCACC							628
Fig.3 SI#5	TGATCGACCAGAAAC	CGATCTCCAATCTGG	GTAACATCCACGCTT	CTAATAACATCATGT	TCAAACCTGGACGGTT	GTCGTGACACTCACC							622
Fig.2 SI#3	TGATCGACCAGAAAC	CGATCTCCAATCTGG	GTAACATCCACGCTT	CTAATAACATCATGT	TCAAACCTGGACGGTT	GTCGTGACACTCACC							619

## Paragraph 3.8

	631	645	646	660	661	675	676	690	691	705	706	720	
As filed	GCTACATCTGGATCA	AATACTTCAATCTGT	TCGACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGACA	ACCAAGTCCAATTCTG							714
Amended	GCTACATCTGGATCA	AATACTTCAATCTGT	TCGACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGACA	ACCAAGTCCAATTCTG							717
Fig.1 SI#1	GCTACATCTGGATCA	AATACTTCAATCTGT	TCGACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGACA	ACCAAGTCCAATTCTG							718
Fig.3 SI#5	GCTACATCTGGATCA	AATACTTCAATCTGT	TCGACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGACA	ACCAAGTCCAATTCTG							712
Fig.2 SI#3	GCTACATCTGGATCA	AATACTTCAATCTGT	TCGACAAAGAACTGA	ACGAAAAAGAAATCA	AAGACCTGTACGACA	ACCAAGTCCAATTCTG							709

## Paragraph 3.9

	721	735	736	750	751	765	766	780	781	795	796	810	
As filed	GTATCCTGAAAGACT	TCTGGGGTGACTACC	TGCAGTACGACAAAC	CGTACTACATGCTGA	ATCTGTACGATCCGA	ACAAATACGTTGACG							804
Amended	GTATCCTGAAAGACT	TCTGGGGTGACTACC	TGCAGTACGACAAAC	CGTACTACATGCTGA	ATCTGTACGATCCGA	ACAAATACGTTGACG							807
Fig.1 SI#1	GTATCCTGAAAGACT	TCTGGGGTGACTACC	TGCAGTACGACAAAC	CGTACTACATGCTGA	ATCTGTACGATCCGA	ACAAATACGTTGACG							808
Fig.3 SI#5	GTATCCTGAAAGACT	TCTGGGGTGACTACC	TGCAGTACGACAAAC	CGTACTACATGCTGA	ATCTGTACGATCCGA	ACAAATACGTTGACG							802
Fig.2 SI#3	GTATCCTGAAAGACT	TCTGGGGTGACTACC	TGCAGTACGACAAAC	CGTACTACATGCTGA	ATCTGTACGATCCGA	ACAAATACGTTGACG							799

## Paragraph 3.10

	811	825	826	840	841	855	856	870	871	885	886	900	
As filed	TCAACAAATGTAGGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGGTTCTGTTATGA	CTACCAACATCTACC	TGAACTCTTCCCTGT							894
Amended	TCAACAAATGTAGGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGGTTCTGTTATGA	CTACCAACATCTACC	TGAACTCTTCCCTGT							897
Fig.1 SI#1	TCAACAAATGTAGGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGGTTCTGTTATGA	CTACCAACATCTACC	TGAACTCTTCCCTGT							898
Fig.3 SI#5	TCAACAAATGTAGGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGGTTCTGTTATGA	CTACCAACATCTACC	TGAACTCTTCCCTGT							892
Fig.2 SI#3	TCAACAAATGTAGGTA	TCCGCGGTTACATGT	ACCTGAAAGGTCCGC	GTGGTTCTGTTATGA	CTACCAACATCTACC	TGAACTCTTCCCTGT							889

## Paragraph 3.11

	901	915	916	930	931	945	946	960	961	975	976	990	
As filed	ACCGTGGTACCAAAT	TCATCATCAAGAAAT	ACGCGTCTGGTAACA	AGGACAATATCGTTC	GCAACAATGATCGTG	TATACATCAATGTTG							981
Amended	ACCGTGGTACCAAAT	TCATCATCAAGAAAT	ACGCGTCTGGTAACA	AGGACAATATCGTTC	GCAACAATGATCGTG	TATACATCAATGTTG							987
Fig.1 SI#1	ACCGTGGTACCAAAT	TCATCATCAAGAAAT	ACGCGTCTGGTAACA	AGGACAATATCGTTC	GCAACAATGATCGTG	TATACATCAATGTTG							988
Fig.3 SI#5	ACCGTGGTACCAAAT	TCATCATCAAGAAAT	ACGCGTCTGGTAACA	AGGACAATATCGTTC	GCAACAATGATCGTG	TATACATCAATGTTG							982
Fig.2 SI#3	ACCGTGGTACCAAAT	TCATCATCAAGAAAT	ACGCGTCTGGTAACA	AGGACAATATCGTTC	GCAACAATGATCGTG	TATACATCAATGTTG							979

## Paragraph 3.12

	991	1005	1006	1020	1021	1035	1036	1050	1051	1065	1066	1080	
As filed	TAGTTAAGAACAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGAGAAAAGA	TCTTGTCTGCTCTGG	AAATCCCGGACGTTG							1071
Amended	TAGTTAAGAACAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGAGAAAAGA	TCTTGTCTGCTCTGG	AAATCCCGGACGTTG							1077
Fig.1 SI#1	TAGTTAAGAACAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGAGAAAAGA	TCTTGTCTGCTCTGG	AAATCCCGGACGTTG							1078
Fig.3 SI#5	TAGTTAAGAACAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGAGAAAAGA	TCTTGTCTGCTCTGG	AAATCCCGGACGTTG							1072
Fig.2 SI#3	TAGTTAAGAACAAG	AATACCGTCTGGCTA	CCAATGCTTCTCAGG	CTGGTGAGAAAAGA	TCTTGTCTGCTCTGG	AAATCCCGGACGTTG							1069

## Paragraph 3.13

	1081	1095	1096	1110	1111	1125	1126	1140	1141	1155	1156	1170	
As filed	GTAATCTGTCTCAGG	TAGTTGTAATGAAAT	CCAAGAACGACCAGG	GTATCACTAACAAAT	GCAAAATGAATCTGC	AGGACAACAATGGTA							1161
Amended	GTAATCTGTCTCAGG	TAGTTGTAATGAAAT	CCAAGAACGACCAGG	GTATCACTAACAAAT	GCAAAATGAATCTGC	AGGACAACAATGGTA							1167
Fig.1 SI#1	GTAATCTGTCTCAGG	TAGTTGTAATGAAAT	CCAAGAACGACCAGG	GTATCACTAACAAAT	GCAAAATGAATCTGC	AGGACAACAATGGTA							1168
Fig.3 SI#5	GTAATCTGTCTCAGG	TAGTTGTAATGAAAT	CCAAGAACGACCAGG	GTATCACTAACAAAT	GCAAAATGAATCTGC	AGGACAACAATGGTA							1162
Fig.2 SI#3	GTAATCTGTCTCAGG	TAGTTGTAATGAAAT	CCAAGAACGACCAGG	GTATCACTAACAAAT	GCAAAATGAATCTGC	AGGACAACAATGGTA							1159

## Paragraph 3.14

	1171	1185	1186	1200	1201	1215	1216	1230	1231	1245	1246	1260	
As filed	ACGATATCGGTTTCA	TCGGTTTCCACCAGT	TCAACAATATCGCTA	AACTGGTTGCTTCCA	ACTGGTACAATCGTC	AGATCGAACGTTCTCT							1251
Amended	ACGATATCGGTTTCA	TCGGTTTCCACCAGT	TCAACAATATCGCTA	AACTGGTTGCTTCCA	ACTGGTACAATCGTC	AGATCGAACGTTCTCT							1257
Fig.1 SI#1	ACGATATCGGTTTCA	TCGGTTTCCACCAGT	TCAACAATATCGCTA	AACTGGTTGCTTCCA	ACTGGTACAATCGTC	AGATCGAACGTTCTCT							1258
Fig.3 SI#5	ACGATATCGGTTTCA	TCGGTTTCCACCAGT	TCAACAATATCGCTA	AACTGGTTGCTTCCA	ACTGGTACAATCGTC	AGATCGAACGTTCTCT							1252
Fig.2 SI#3	ACGATATCGGTTTCA	TCGGTTTCCACCAGT	TCAACAATATCGCTA	AACTGGTTGCTTCCA	ACTGGTACAATCGTC	AGATCGAACGTTCTCT							1249

Paragraph 3.15

	1261	1275	1276	1290	1291	1305	1306	1320	1321	1335	1336	1350
As filed	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA	TCCCGGTTGATGACG	GTTGGGGTGAACGTC	CGCTGTAACCCGGA	AAGCTT						1332
Amended	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA	TCCCGGTTGATGACG	GTTGGGGTGAACGTC	CGCTGTAACCCGGA	AAGCTT						1338
Fig.1 SI#1	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA	TCCCGGTTGATGACG	GTTGGGGTGAACGTC	CGCTGTAAGAATTC-	-----						1332
Fig.3 SI#5	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA	TCCCGGTTGATGACG	GTTGGGGTGAACGTC	CGCTGTAAGAATTC-	-----						1326
Fig.2 SI#3	CTCGCACTCTGGGTT	GCTCTTGGGAGTTCA	TCCCGGTTGATGACG	GTTGGGGTGAACGTC	CGCTGTAAGAATTC-	-----						1323

**Alignment 4**

SEQ ID NO:40 (appearing on page 38 in the specification as filed) has been amended as

follows:

At position 121 of paragraph 4.2, T→I.

At position 327 of paragraph 4.4, Q→W.

At position 334 of paragraph 4.4, K→Y.

*Original*  
*Start*  
*End*  
*Amended*

Paragraph 4.1	1	15	16	30	31	45	46	60	61	75	76	90	
As filed	-FNKYNSEILNNIIL	NLRYKDN	NLIDLSGY	GAKVEYD	GV	VELNDK	NQFKLTSSANSKIRV	TQNQNIIFNSVFLDF	SVSFWIRIPKYKNDG				89
Amended	-FNKYNSEILNNIIL	NLRYKDN	NLIDLSGY	GAKVEYD	GV	VELNDK	NQFKLTSSANSKIRV	TQNQNIIFNSVFLDF	SVSFWIRIPKYKNDG				89
Fig 4 SI#8	MANKYNSEILNNIIL	NLRYKDN	NLIDLSGY	GAKVEYD	GV	VELNDK	NQFKLTSSANSKIRV	TQNQNIIFNSVFLDF	SVSFWIRIPKYKNDG				90
Ac# M81186	MFNKYNSEILNNIIL	NLRYKDN	NLIDLSGY	GAKVEYD	GV	VELNDK	NQFKLTSSANSKIRV	TQNQNIIFNSVFLDF	SVSFWIRIPKYKNDG				90

Paragraph 4.2	91	105	106	120	121	135	136	150	151	165	166	180	
As filed	IQNYIHNEYTIINC	M	KNSGWKISIRGNRI	ITWTLIDINGKTKSVF	FEYNIRE	DISEYINR	WFFVTITNNLNNAKI	YINGKLESNTDIKDI					179
Amended	IQNYIHNEYTIINC	M	KNSGWKISIRGNRI	ITWTLIDINGKTKSVF	FEYNIRE	DISEYINR	WFFVTITNNLNNAKI	YINGKLESNTDIKDI					179
Fig 4 SI#8	IQNYIHNEYTIINC	M	KNSGWKISIRGNRI	ITWTLIDINGKTKSVF	FEYNIRE	DISEYINR	WFFVTITNNLNNAKI	YINGKLESNTDIKDI					180
Ac# M81186	IQNYIHNEYTIINC	M	KNSGWKISIRGNRI	ITWTLIDINGKTKSVF	FEYNIRE	DISEYINR	WFFVTITNNLNNAKI	YINGKLESNTDIKDI					180

Paragraph 4.3	181	195	196	210	211	225	226	240	241	255	256	270	
As filed	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQS	NIEERYK	IQSYSEYLKDFWGNP	LMYNKEYYMFNAGNK	NSYIKLKKDSPVGEI						269
Amended	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQS	NIEERYK	IQSYSEYLKDFWGNP	LMYNKEYYMFNAGNK	NSYIKLKKDSPVGEI						269
Fig 4 SI#8	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQS	NIEERYK	IQSYSEYLKDFWGNP	LMYNKEYYMFNAGNK	NSYIKLKKDSPVGEI						270
Ac# M81186	REVIANGEIIFKLDG	DIDRTQFIWMKYFSI	FNTELSQS	NIEERYK	IQSYSEYLKDFWGNP	LMYNKEYYMFNAGNK	NSYIKLKKDSPVGEI						270

Paragraph 4.4	271	285	286	300	301	315	316	330	331	345	346	360	
As filed	LTRSKYNQNSKYINY	RDLYIG	EKFII	RRKS	NSQSINDDIVRKEDY	IYLDFFNLNQEQRVY	TYKKFKKEEEKLFLA	PISDSDEFYNTIQIK					359
Amended	LTRSKYNQNSKYINY	RDLYIG	EKFII	RRKS	NSQSINDDIVRKEDY	IYLDFFNLNQEQRVY	TYKYFKKEEEKLFLA	PISDSDEFYNTIQIK					359
Fig 4 SI#8	LTRSKYNQNSKYINY	RDLYIG	EKFII	RRKS	NSQSINDDIVRKEDY	IYLDFFNLNQEQRVY	TYKYFKKEEEKLFLA	PISDSDEFYNTIQIK					360
Ac# M81186	LTRSKYNQNSKYINY	RDLYIG	EKFII	RRKS	NSQSINDDIVRKEDY	IYLDFFNLNQEQRVY	TYKYFKKEEEKLFLA	PISDSDEFYNTIQIK					360

Paragraph 4.5	361	375	376	390	391	405	406	420	421	435	436	450	
As filed	EYDEQPTYSCQLLFK	KDEESTDEIGLIGIH	RFYESGIVFEEYKDY	FCISKWYLKEVKKRP	YNLKLGCNWQFIPKD	EGWTE							439
Amended	EYDEQPTYSCQLLFK	KDEESTDEIGLIGIH	RFYESGIVFEEYKDY	FCISKWYLKEVKKRP	YNLKLGCNWQFIPKD	EGWTE							439
Fig 4 SI#8	EYDEQPTYSCQLLFK	KDEESTDEIGLIGIH	RFYESGIVFEEYKDY	FCISKWYLKEVKKRP	YNLKLGCNWQFIPKD	EGWTE							440
Ac# M81186	EYDEQPTYSCQLLFK	KDEESTDEIGLIGIH	RFYESGIVFEEYKDY	FCISKWYLKEVKKRP	YNLKLGCNWQFIPKD	EGWTE							440

**Alignment 5**

SEQ ID NO:39 (appearing on page 39 in the specification as filed) has been amended as

follows:

At positions 15-17 of paragraph 5.1, TTT is deleted;

At position 820 of paragraph 5.10, A is inserted;

At position 933 of paragraph 5.11, T is inserted;

At position 988 of paragraph 5.11, G is inserted; and

At position 1226 of paragraph 5.14, A is inserted.

SEQ ID NO:7 (appearing in Figure 4 of the specification as filed) has been amended as

follows:

At position 255 of paragraph 5.3, T→C.

**Paragraph 5.1**

	1	15 16	30 31	45 46	60 61	75 76	90	
Fig 4 as filed	GAATTCACGATGGC-	--CAACAAATACAAT	TCCGAAATCCTGAAC	AATATCATCCTGAAC	CTGCGTTACAAAGAC	AACAATCTGATCGAT		87
Fig4 corrected	GAATTCACGATGGC-	--CAACAAATACAAT	TCCGAAATCCTGAAC	AATATCATCCTGAAC	CTGCGTTACAAAGAC	AACAATCTGATCGAT		87
P.39 corrected	-----ATGGC-	--CAACAAATACAAT	TCCGAAATCCTGAAC	AATATCATCCTGAAC	CTGCGTTACAAAGAC	AACAATCTGATCGAT		78
P.39 as filed	-----ATGGCT	TTCAACAAATACAAT	TCCGAAATCCTGAAC	AATATCATCCTGAAC	CTGCGTTACAAAGAC	AACAATCTGATCGAT		81

**Paragraph 5.2**

	91	105 106	120 121	135 136	150 151	165 166	180	
Fig 4 as filed	CTGTCTGGTTACGGT	GCTAAAGTTGAAGTA	TACGACGGTGTGAA	CTGAATGACAAGAAC	CAGTTCAAACGTACC	TCTTCCGCTAACTCT		177
Fig4 corrected	CTGTCTGGTTACGGT	GCTAAAGTTGAAGTA	TACGACGGTGTGAA	CTGAATGACAAGAAC	CAGTTCAAACGTACC	TCTTCCGCTAACTCT		177
P.39 corrected	CTGTCTGGTTACGGT	GCTAAAGTTGAAGTA	TACGACGGTGTGAA	CTGAATGACAAGAAC	CAGTTCAAACGTACC	TCTTCCGCTAACTCT		168
P.39 as filed	CTGTCTGGTTACGGT	GCTAAAGTTGAAGTA	TACGACGGTGTGAA	CTGAATGACAAGAAC	CAGTTCAAACGTACC	TCTTCCGCTAACTCT		171

**Paragraph 5.3**

	181	195 196	210 211	225 226	240 241	255 256	270	
Fig 4 as filed	AAGATCCGTGTTACT	CAGAATCAGAACATC	ATCTTCAACTCCGTA	TTCTGGACTTCTCT	GTTTCCTTCTGGATT	CGTATCCCGAAATAC		267
Fig4 corrected	AAGATCCGTGTTACT	CAGAATCAGAACATC	ATCTTCAACTCCGTA	TTCTGGACTTCTCT	GTTTCCTTCTGGATT	CGTATCCCGAAATAC		267
P.39 corrected	AAGATCCGTGTTACT	CAGAATCAGAACATC	ATCTTCAACTCCGTA	TTCTGGACTTCTCT	GTTTCCTTCTGGATT	CGTATCCCGAAATAC		258
P.39 as filed	AAGATCCGTGTTACT	CAGAATCAGAACATC	ATCTTCAACTCCGTA	TTCTGGACTTCTCT	GTTTCCTTCTGGATT	CGTATCCCGAAATAC		261

**Paragraph 5.4**

	271	285 286	300 301	315 316	330 331	345 346	360	
Fig 4 as filed	AAGAACGACGGTATC	CAGAATTACATCCAC	AATGAATACACCATC	ATCAACTGCATGAAG	AATAACTCTGGTTGG	AAGATCTCCATCCGC		357
Fig4 corrected	AAGAACGACGGTATC	CAGAATTACATCCAC	AATGAATACACCATC	ATCAACTGCATGAAG	AATAACTCTGGTTGG	AAGATCTCCATCCGC		357
P.39 corrected	AAGAACGACGGTATC	CAGAATTACATCCAC	AATGAATACACCATC	ATCAACTGCATGAAG	AATAACTCTGGTTGG	AAGATCTCCATCCGC		348
P.39 as filed	AAGAACGACGGTATC	CAGAATTACATCCAC	AATGAATACACCATC	ATCAACTGCATGAAG	AATAACTCTGGTTGG	AAGATCTCCATCCGC		351



## Paragraph 5.5

	361	375	376	390	391	405	406	420	421	435	436	450	
Fig 4 as filed	GGTAACCGTATCATC	TGGACTCTGATCGAT	ATCAACGGTAAGACC	AAATCTGTATTCTTC	GAATACAACATCCGT	GAAGACATCTCTGAA	447						
Fig4 corrected	GGTAACCGTATCATC	TGGACTCTGATCGAT	ATCAACGGTAAGACC	AAATCTGTATTCTTC	GAATACAACATCCGT	GAAGACATCTCTGAA	447						
P.39 corrected	GGTAACCGTATCATC	TGGACTCTGATCGAT	ATCAACGGTAAGACC	AAATCTGTATTCTTC	GAATACAACATCCGT	GAAGACATCTCTGAA	438						
P.39 as filed	GGTAACCGTATCATC	TGGACTCTGATCGAT	ATCAACGGTAAGACC	AAATCTGTATTCTTC	GAATACAACATCCGT	GAAGACATCTCTGAA	441						

## Paragraph 5.6

	451	465	466	480	481	495	496	510	511	525	526	540	
Fig 4 as filed	TACATCAATCGCTGG	TTCTTCGTTACCATC	ACCAATAAACCCTGAAC	AATGCTAAAAATCTAC	ATCAACGGTAAACTG	GAATCTAATACCGAC	537						
Fig4 corrected	TACATCAATCGCTGG	TTCTTCGTTACCATC	ACCAATAAACCCTGAAC	AATGCTAAAAATCTAC	ATCAACGGTAAACTG	GAATCTAATACCGAC	537						
P.39 corrected	TACATCAATCGCTGG	TTCTTCGTTACCATC	ACCAATAAACCCTGAAC	AATGCTAAAAATCTAC	ATCAACGGTAAACTG	GAATCTAATACCGAC	528						
P.39 as filed	TACATCAATCGCTGG	TTCTTCGTTACCATC	ACCAATAAACCCTGAAC	AATGCTAAAAATCTAC	ATCAACGGTAAACTG	GAATCTAATACCGAC	531						

## Paragraph 5.7

	541	555	556	570	571	585	586	600	601	615	616	630	
Fig 4 as filed	ATCAAAGACATCCGT	GAAGTTATCGCTAAC	GGTGAAATCATCTTC	AAACTGGACGGTGAC	ATCGATCGTACCCAG	TTCATCTGGATGAAA	627						
Fig4 corrected	ATCAAAGACATCCGT	GAAGTTATCGCTAAC	GGTGAAATCATCTTC	AAACTGGACGGTGAC	ATCGATCGTACCCAG	TTCATCTGGATGAAA	627						
P.39 corrected	ATCAAAGACATCCGT	GAAGTTATCGCTAAC	GGTGAAATCATCTTC	AAACTGGACGGTGAC	ATCGATCGTACCCAG	TTCATCTGGATGAAA	618						
P.39 as filed	ATCAAAGACATCCGT	GAAGTTATCGCTAAC	GGTGAAATCATCTTC	AAACTGGACGGTGAC	ATCGATCGTACCCAG	TTCATCTGGATGAAA	621						

## Paragraph 5.8

	631	645	646	660	661	675	676	690	691	705	706	720	
Fig 4 as filed	TACTTCTCCATCTTC	AACACCGAACTGTCT	CAGTCCAATATCGAA	GAACGGTACAAGATC	CAGTCTTACTCCGAA	TACCTGAAAGACTTC	717						
Fig4 corrected	TACTTCTCCATCTTC	AACACCGAACTGTCT	CAGTCCAATATCGAA	GAACGGTACAAGATC	CAGTCTTACTCCGAA	TACCTGAAAGACTTC	717						
P.39 corrected	TACTTCTCCATCTTC	AACACCGAACTGTCT	CAGTCCAATATCGAA	GAACGGTACAAGATC	CAGTCTTACTCCGAA	TACCTGAAAGACTTC	708						
P.39 as filed	TACTTCTCCATCTTC	AACACCGAACTGTCT	CAGTCCAATATCGAA	GAACGGTACAAGATC	CAGTCTTACTCCGAA	TACCTGAAAGACTTC	711						

## Paragraph 5.9

	721	735	736	750	751	765	766	780	781	795	796	810	
Fig 4 as filed	TGGGGTAATCCGCTG	ATGTACAACAAGAA	TACTATATGTTCAAT	GCTGGTAACAAGAAC	TCTTACATCAAACCTG	AAGAAAGACTCTCCG	807						
Fig4 corrected	TGGGGTAATCCGCTG	ATGTACAACAAGAA	TACTATATGTTCAAT	GCTGGTAACAAGAAC	TCTTACATCAAACCTG	AAGAAAGACTCTCCG	807						
P.39 corrected	TGGGGTAATCCGCTG	ATGTACAACAAGAA	TACTATATGTTCAAT	GCTGGTAACAAGAAC	TCTTACATCAAACCTG	AAGAAAGACTCTCCG	798						
P.39 as filed	TGGGGTAATCCGCTG	ATGTACAACAAGAA	TACTATATGTTCAAT	GCTGGTAACAAGAAC	TCTTACATCAAACCTG	AAGAAAGACTCTCCG	801						

## Paragraph 5.10

	811	825	826	840	841	855	856	870	871	885	886	900	
Fig 4 as filed	GTTGGTGAAATCCCTG	ACTCGTTCCAAATAC	AACCAGAACTCTAAA	TACATCAACTACCGC	GACCTGTACATCCGT	GAAAAGTTCATCATC	897						
Fig4 corrected	GTTGGTGAAATCCCTG	ACTCGTTCCAAATAC	AACCAGAACTCTAAA	TACATCAACTACCGC	GACCTGTACATCCGT	GAAAAGTTCATCATC	897						
P.39 corrected	GTTGGTGAAATCCCTG	ACTCGTTCCAAATAC	AACCAGAACTCTAAA	TACATCAACTACCGC	GACCTGTACATCCGT	GAAAAGTTCATCATC	888						
P.39 as filed	GTTGGTGAAATCCCTG	ACTCGTTCCAAATAC	AACCAGAACTCTAAA	TACATCAACTACCGC	GACCTGTACATCCGT	GAAAAGTTCATCATC	890						

## Paragraph 5.11

	901	915	916	930	931	945	946	960	961	975	976	990	
Fig 4 as filed	CGTCGCAAATCTAAC	TCTCAGTCCATCAAT	GATGACATCGTACGT	AAAGAAGACTACATC	TACCTGGACTTCTTC	AACCTGAATCAGGAA	987						
Fig4 corrected	CGTCGCAAATCTAAC	TCTCAGTCCATCAAT	GATGACATCGTACGT	AAAGAAGACTACATC	TACCTGGACTTCTTC	AACCTGAATCAGGAA	987						
P.39 corrected	CGTCGCAAATCTAAC	TCTCAGTCCATCAAT	GATGACATCGTACGT	AAAGAAGACTACATC	TACCTGGACTTCTTC	AACCTGAATCAGGAA	978						
P.39 as filed	CGTCGCAAATCTAAC	TCTCAGTCCATCAAT	GA-GACATCGTACGT	AAAGAAGACTACATC	TACCTGGACTTCTTC	AACCTGAATCAG-AA	978						

## Paragraph 5.12

	991	1005	1006	1020	1021	1035	1036	1050	1051	1065	1066	1080	
Fig 4 as filed	TGGCGTGATACACC	TACAAGTACTTCAAG	AAAGAAGAAGAAAAG	CTTTTCCTGGCTCCG	ATCTCTGATTCCGAC	GAACCTCTACAACACC	1077						
Fig4 corrected	TGGCGTGATACACC	TACAAGTACTTCAAG	AAAGAAGAAGAAAAG	CTTTTCCTGGCTCCG	ATCTCTGATTCCGAC	GAACCTCTACAACACC	1077						
P.39 corrected	TGGCGTGATACACC	TACAAGTACTTCAAG	AAAGAAGAAGAAAAG	CTTTTCCTGGCTCCG	ATCTCTGATTCCGAC	GAACCTCTACAACACC	1068						
P.39 as filed	TGGCGTGATACACC	TACAAGTACTTCAAG	AAAGAAGAAGAAAAG	CTTTTCCTGGCTCCG	ATCTCTGATTCCGAC	GAACCTCTACAACACC	1068						

## Paragraph 5.13

	1081	1095	1096	1110	1111	1125	1126	1140	1141	1155	1156	1170	
Fig 4 as filed	ATCCAGATCAAAGAA	TACGACGAACAGCCG	ACCTACTCTTGCCAG	CTGCTGTTCAAGAAA	GATGAAGAACTTACT	GACGAAATCCGTCTG	1167						
Fig4 corrected	ATCCAGATCAAAGAA	TACGACGAACAGCCG	ACCTACTCTTGCCAG	CTGCTGTTCAAGAAA	GATGAAGAACTTACT	GACGAAATCCGTCTG	1167						
P.39 corrected	ATCCAGATCAAAGAA	TACGACGAACAGCCG	ACCTACTCTTGCCAG	CTGCTGTTCAAGAAA	GATGAAGAACTTACT	GACGAAATCCGTCTG	1158						
P.39 as filed	ATCCAGATCAAAGAA	TACGACGAACAGCCG	ACCTACTCTTGCCAG	CTGCTGTTCAAGAAA	GATGAAGAACTTACT	GACGAAATCCGTCTG	1158						

## Paragraph 5.14

	1171	1185	1186	1200	1201	1215	1216	1230	1231	1245	1246	1260	
Fig 4 as filed	ATCCGTATCCACCGT	TTCTACGAATCTGGT	ATCGTATTGGAAGAA	TACAAAGACTACTTC	TGCATCTCCAAATGG	TACCTGAAGGAAGTT	1257						
Fig4 corrected	ATCCGTATCCACCGT	TTCTACGAATCTGGT	ATCGTATTGGAAGAA	TACAAAGACTACTTC	TGCATCTCCAAATGG	TACCTGAAGGAAGTT	1257						
P.39 corrected	ATCCGTATCCACCGT	TTCTACGAATCTGGT	ATCGTATTGGAAGAA	TACAAAGACTACTTC	TGCATCTCCAAATGG	TACCTGAAGGAAGTT	1248						
P.39 as filed	ATCCGTATCCACCGT	TTCTACGAATCTGGT	ATCGTATTGGAAGAA	TACAAAGACT-CTTC	TGCATCTCCAAATGG	TACCTGAAGGAAGTT	1247						

Paragraph 5.15

	1261	1275 1276	1290 1291	1305 1306	1320 1321	1335 1336	1350	
Fig 4 as filed	AAACGCAAACCGTAC	AACCTGAAACTGGGT	TGCAATTGGCAGTTC	ATCCCGAAAGACGAA	GGTTGGACCGAATAG	TAAGAATTC-----	1341	
Fig4 corrected	AAACGCAAACCGTAC	AACCTGAAACTGGGT	TGCAATTGGCAGTTC	ATCCCGAAAGACGAA	GGTTGGACCGAATAG	TAAGAATTC-----	1341	
P.39 corrected	AAACGCAAACCGTAC	AACCTGAAACTGGGT	TGCAATTGGCAGTTC	ATCCCGAAAGACGAA	GGTTGGACCGAATAG	TAACCTCTAGAGTCG	1338	
P.39 as filed	AAACGCAAACCGTAC	AACCTGAAACTGGGT	TGCAATTGGCAGTTC	ATCCCGAAAGACGAA	GGTTGGACCGAATAG	TAACCTCTAGAGTCG	1337	

Paragraph 5.16

	1351	1365 1366	1380 1381	1395 1396	1410 1411	1425 1426	1440
Fig 4 as filed	-----	1341					
Fig4 corrected	-----	1341					
P.39 corrected	AGGCCTGCAG	1348					
P.39 as filed	AGGCCTGCAG	1347					

ALIGNMENTS IN RESPONSE TO REJECTIONS UNDER 35 U.S.C. §102Alignment 6

Smith SEQ ID NO:7 (hereinafter "Smith7\_186") was aligned with the nucleotide sequence of Campbell Eklund 2B (as shown in Figure 2, Campbell page 2258; hereinafter "Cbl\_Ek2B"). The primer sequence shown on Campbell page 2256 (Table 2) is depicted here in red letters. Nucleotides 873-1084 of Cbl\_Ek2B, to which the Examiner has referred, are depicted here in blue. Identical nucleotides are marked by an asterix highlighted in yellow.

```
Smith7_186      GAATTACGATGGCCAAACAAATACAATCCGAAATCCTGAACAATATCATCCTGAACCTGCGTTACAAAGACAACAACTGATCGATCTGTCTGGTTACGGTGTAAAGTTGAAGTATAC 120
Cbl_Ek2B      -----

Smith7_186      GACGGTGTGAACCTGAATGACAAGAACCCAGTTCAAACCTGACCTCTCCGCTAACTCTAAGATCCGTGTTACTCAGAATCAGAACATCATCTTCAACTCCGTATTCCTGGACTTCTCTGTT 240
Cbl_Ek2B      -----AACAGCTAAAGGAAATTTTGAAAGTGCTTTTGAG---ATTGCAGGATCCAGTATTTT---ACTAGAATTTATACCAGAACTTTAAATACCTGTAGTTGGAGTCT 98
              * * * * *

Smith7_186      TCCTTCTGGAATCCGTATCCGAAATACAAGAACGACGGTATCCAGAAATTACATCCACAATGAATACACCATCATCAACTGCATGAAGAATAAATCTGGTTGGAAGATCTCCATCCCGGGT 360
Cbl_Ek2B      TTTTATTAGAATCATATATTGACA-ATAAAAA-----TAAAAATTATTAACAATAGATAATGCTT---TAACTAAAAGAGTGGAATAATGGATTGATA-----TGTACGGATT 198
              * * * * *

Smith7_186      AACCGTATCATCTGGACTCTGATCGATATCAACGGTAAAGACCAAACTGTATCTTCGAATACAACATCCGTGAAGACATCTCTGAATACATCAATCGCTGGTTCTTCGTTACCATCACC 480
Cbl_Ek2B      AATAGTAGCGCAATGGCTCTCAACAGT-----TAATACTCAATTTTATACAATAAAGAGGGAATGTATAAGG---CTTTAAAT-TATCAAGCACAAAGCA-TTGGAAAGAAATAATA 304
              * * * * *

Smith7_186      AATAACCTGAACAATGCTAAAACTACATCAACGGTAACTGGAATCTAAATCCGACATCAAGACATCCGTGAAGTTATCGTAAACGGTGAAATCATCTTCAAACCTGGACGGTGACATC 600
Cbl_Ek2B      AAATACAAATATAATA-TATATCTGAA--GAGGAAAAGTCAAATATTAACTCAATTTTAAATGATATA--AATTCATAACTTAATGATGGTATTAAAC--CAAGCTATG-GATAATATA 415
              * * * * *

Smith7_186      GATCGTACCCAGTTCATCTGGATGAA-ATATCTCTCCATCTTCAAC-ACCGAACTGTCTCAGTCCAATATCGAAGAACGGTACAAGA-TCCAGTCTTACTCCGAATACCTGAAAGACTTC 717
Cbl_Ek2B      AAT-----GATTTTATAAATGAATGTTCTGTATCATATTTAATGAAAAAATGATTCATTAGCTGTAAAAAAT--TACTAGACTTTGATAATACTCTCAA-----AAAAAATTTA 520
              * * * * *

Smith7_186      TGGGGTAATCCGCTGATGTACAACAAAGAACTACTATATGTTCAATGCTGGTAAACAAGAACTCTTACATCAAACCTGAAGAAAGACTCTCCGGTTGGTGAATCTGACTCGTTCCAAATAC 837
Cbl_Ek2B      TTAAATTATATA--GATGAA-AAATAATTATATTTAAATTGGAAGGTGAGAAGATGAAAAATCA-----AAAGTAGATAAATACT-----TGAAACC-----ATT-----ATAC 611
              * * * * *

Smith7_186      AACCAGAACTCTAAATACATCAACTACCGGACCTGTACATCGGTGAAAAGTTCAATCATCCGTCCGAAATCTAACTCTCAGTCCATCAATGATGACATCGTAAAGAAAGACTACATC 957
Cbl_Ek2B      CATTTGATCTTTCAACGTAT-----ACTAATAATGAAATCTAAT-AAAAATATTTAATAAATAAATAGCGAAATTTTAAATAATATTATCTTTAAATTTAAGATATAGA-GATAATAAT 724
              * * * * *

Smith7_186      TACCTGGACTTCTTCAACCTGAATCAGGAATGGCGTGTATACACCTACAAGTACTTCAAGAAAGAAAGAAAGCTTTTCTTGGCTCCGATCTTGATTCGGACGAATCTTACAACACC 1077
Cbl_Ek2B      TTAATAGATTTT-----ATCAGGATATGGAGCAAG-GTAGAGGTATATGATGGGGTCAAGCTTAATGATAAAAAATCAATTTAAATTAAGTATAGTAAAGATTAGAGTCAC- 837
              * * * * *

Smith7_186      ATCCAGATCAAAGAAT-ACGACGAACAGCCGA---CCTACTCTTGGCAGCTGTCTTCAAGAAAGATGAA-GAATCTACTGACGAAATCGGTCTGATCGGTATCCACCGTTTCTACGAAT 1192
Cbl_Ek2B      -TCAAAATCAGAATATTATATTAAATAGTATGTTCTTGATTTTAGCGTTAGCTTTTGGATAAGGATACCTAAATATAGGAATGATGATATACAAAATTTATATTATTAATGAATATACGA 956
              * * * * *

Smith7_186      CTGGTATCGTATTCGAAGAATA-CAAAGACTACTTCTGCATCTCCAAATGGTACCTGAAGGAAGTTAAACGCAAAACCGTACAACCTGAAA--CTGGGTGCAATTGGCAGTTTATCCCGA 1309
Cbl_Ek2B      TAATTAAAT-TGTATGAAAAATAATTCAGGCTGGAAA-ATATCTATTAGGGGTAAATAGGATAAATGGACCTTAAATGATATAAATGGAAAAACCAATCAGTATTTTTTGAATATAACAT 1074
              * * * * *

Smith7_186      AAGACGAAGGTTGGACCGAATAGTAAGAATTC 1341
Cbl_Ek2B      AAGA-GAAGAT----- 1084
              * * * * *
```

## Alignment 7

Smith SEQ ID NO:8 (hereinafter "Smith8\_186") was aligned with the amino acid sequence of Campbell Eklund 2B (as shown in Figure 2, Campbell page 2258; hereinafter "Cbl\_Ek2B"). Identical amino acids are marked by an asterisk highlighted in yellow.

```

Smith8_186  MANKYNSEILNIIILNRYKDNLLIDLSGYGAKVEVDGVELNDKNQPKLTSSANSKIRVTQNQNIIFNSVPLDFSVSWIRIPKYKNDGIONYIHNEYTIINCMKNNSGWKISIRGNRI 120
Cbl_Ek2B      -----TAKGNFESAPEIAGSSILLEFIPELLIPVVGVPFLLESYIDNKNKIITIDNALTNRVEKWIDMYGLIVAQWLS----TVNTQFYTIKEGMYKALNYQAQALEEII 101
              *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *
Smith8_186  IWTLLIDINGKTKSVFFEYNIREDISSEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVIANGEIIFKLDGDIIDRTQPIWMKYFSIFNTELSQSNIEERYKIQSYSEYKDFWGNP 240
Cbl_Ek2B      KYKYNISSEEEKS-----NININFND-INSKLNDGINQAMDNINDFIN---ECSVSYLMKKMIPLAVKKLLDFDNTLKKNLLNYIDENKLY---LIGSVEDEKSKVDKYLKTIIPFDLS- 208
              *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *
Smith8_186  LMYNKEYYMPNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINVRDLYIGEKPPIRRKSNSSQSIINDDIVRKEDYIYLDFFNLNQEWVRVYTYKYFKKEEEKLPLAPISDSDELYNTIQIK 360
Cbl_Ek2B      -TYTNNEILIKIFNKYNSEILN-NIILNLRIRDNNLIDLSCYGAKVEVDGVELNDKNQPKLTSSADSKIRVTQNQNIIFNSMFLDFSVSWIRIPKYRNDDIQNYIHNEYTIINCMKNN 326
              *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *
Smith8_186  EYDEQPTYSCQLLFKKDEESTDEIGLIGIRFYESGIVFEEYKDYFCISKWYLKEVKKRPYNLKLGCNWQFIPKDEGWTE 440
Cbl_Ek2B      SGWKISIRGNRIIWT-----LIDINGKTKS--VFFEYN-----IRED----- 361
              *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *

```

**Alignment 8**

Smith SEQ ID NO:7 (hereinafter "Smith7\_186") was aligned with the nucleotide sequence of Campbell NCTC 7273 (as shown in Figure 2, Campbell page 2258; hereinafter "Cbl\_NCTC"). The primer sequence shown on Campbell page 2256 (Table 2) is depicted here in red letters. Nucleotides 873-1084 of Cbl\_Ek2B, to which the Examiner referred, are depicted here in blue. Identical nucleotides are marked by an asterisk highlighted in yellow.

```
Smith7_186      GAATTCACGATGGCCAACAAATACAATTCGGAATCCTGAACAATATCATCCTGAACCTGCGTTACAAAGACAACAATCTGATCGATCTGTCTGGTTACGGTGCTAAAGTTGAAGTATAC 120
Cbl_NCTC

Smith7_186      GACGGTGTGAAGTGAATGACAAGAACCAGTTCAAACAGACCTCTCCGCTAACTCTAAGATCCGTGTTACTCAGAAACAGAACATCATCTTCAACTCCGTATTCCTGGACTCTCTGTT 240
Cbl_NCTC      -----AACAGCTAAAGGAAATTTTGA--AAATGCTTTTGAGATTGCAGGAGCCAGTATTCT-----ACTAGAATTATACCAGAACTTTTAATACCTGTATTTGGAGCCT 98
                * * * * *

Smith7_186      TCCTTCTGGATCCGTATCCCGAAATACAAGAACGCGGTATCCAGAATTACATCCACAATGAATACACCATCATCAACTGCATGAAGAATAACTCTGGTTGGAAGATCTCCATCCGCGGT 360
Cbl_NCTC      TTTTATTAGAATCATATATTG-----ACAAATAAAAAATAAAATT--ATTAAAAAATAGATAATGCTTTAAC--TAAAGAAATGAAAAAT-----GGAGTGATATGTACGGATT 198
                * * * * *

Smith7_186      AACCGTATCATCTGGACTCTGATCGATATCAACGGTAAGACCAAAATCTGTATTCTTCGAATACAACATCCGTGAAGACA'TCTCTGAATACATCAATCGCTGGTTCTTCGTTACCATCACC 480
Cbl_NCTC      AATAGTAGCGCAATGGCTCTCAACAGT-----TAATACTCAATTTTATACAATAAAGAGGGAAATGATAAGG-----CTTTAAAT-TATCAAGCACAAAGCA--TTGGAGAAATAATA 304
                * * * * *

Smith7_186      AATAACCTGAACAATGCTAAAACTTACATCAACGGTAAACTGGAATCTAATACCGACATCAAGACATCCGTGAAGTTATCGCTAACGGTGAATCATCTTCAAACGGACGGTGACATC 600
Cbl_NCTC      AAATACAGATATAATA-TATATTCTGAA--AAAGAAAAGTCAAAATATTAAACATCGATTTTAATGATATA---AATTC'AAAC'TTAATGAGGGTATTAACT--CAAGCTATA-GATAATATA 415
                * * * * *

Smith7_186      GATCGTACCCAGTTTATCTGGATGAAATACTTCTCCATCTTCAAC-ACCGAAGTGTCTCAGTCCAATATCGAAGAACGGTACAAGA-TCCAGTCTTACTCCGAATACCTGAAAGACTTCT 718
Cbl_NCTC      AATAATTTT---TATAAATGGATG--TTCGTATCATATTTAATGAAAAAATGATTCCATTAGCTGTGAAAAAAT--TACTAGACTTTGATAATACTCTCAA-----AAAAAATTTGT 521
                * * * * *

Smith7_186      GGGGTAATCCGCTGATGTACAACAAGAATACTATATGTTCAATGCTGGTAAACAAGAACTCTTACATCAAAC'GAAGAAAGACTCTCCGGTTGGTGAAATCCTGACTCGTTCCAATATACA 838
Cbl_NCTC      TAAATTATATA--GATGAA-AAATAATTATATTGATTGGAAGTGCAGAAATAGAAAAATCA-----AAAGTAAATAAATACTTGAAAACCATATGCGGTTTGATCTTTCAATATATA 632
                * * * * *

Smith7_186      ACCAGAACTCTAAATACATCAACTACCGGACCTGTACATCGGTGAAAGTTCA'CATCCGTCGAAATCTAAC'TCTCAGTCCATCAATGATGACATCGTACGTAAAGAAAGACTACATCT 958
Cbl_NCTC      CCAATGATACAATACTAATAGAAATGTTTAAATAAATATAATAGCGAAATTTTAAATAATATT-----ATCTTAAATTTAAGATAT-AAGGATAAAT--ATTTAA-----TAGATTT 735
                * * * * *

Smith7_186      ACCTGGACTTCTTCAAACCTGAATCAGGAATGGCGGTATATACACCTACAAGTACTTCAAGAAAAGAAAGAAAGCTTTTCTGGCTCCG--ATCTCTGATTCGGACGAACCTTACAACA 1075
Cbl_NCTC      ATCAGGATATG-----GGGCAAGGTAGAGGTATATG-ATGGAGTCGAGCTTAATGATAAAAA'TCAATTTAAATTTAACTAGTTCAGCAATAGTAAGATTAGAGTGACTCAAAATCA 846
                * * * * *

Smith7_186      CCAT-CCAGATCAAAGAATACGACGAACAGCGACCTACTCTTGCCAGCTGCTGTCAAGAAAGATGAAGAATCTACTGACGAAATCGGTCTGATCGGTATCCACCGTTTCTACGAATCT 1194
Cbl_NCTC      GAATATCATATTTAATAGTGTGTT-----CCTTGATTTTAGCTTTAGCTTTTGGAATAAGAATACCTAA--ATATAAGAATGATGGTATACAAAATTATATTCATTAATGAATATACAATA 958
                * * * * *

Smith7_186      GGTATCGTATTCAAGAATACAAAGACTACTTCTGCATCTCCAAATGGTACCTGAAGGAAGTTAAACGCAACCGTACAACCTGAAA--CTGGGTGCAATTTGGCAGTTTATCCCGAAAG 1312
Cbl_NCTC      ATTAAT-TGTATGAAAAATATTCGGGCTGAAAAATATCTATTAGGGGTAATAGGATAATATGGACTTTAATTGATATAAATGAAAAACCAAAATCGGTATTTTGTGAATATAACATAAG 1077
                * * * * *

Smith7_186      ACGAAGGTTGGACCGAATAGTAAGAATTC 1341
Cbl_NCTC      A-GAAGAT----- 1084
                * * * * *
```

## Alignment 9

Smith SEQ ID NO:8 (hereinafter "Smith8\_186") was aligned with the amino acid sequence of Campbell NCTC 7273 (as shown in Figure 2, Campbell page 2258; hereinafter "Cbl\_NCTC").

Identical amino acids are marked by an asterisk highlighted in yellow.

```

Smith8_186  MANKYNSEILNIIILNRYKDNILDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIRVTQNQNIIFNSVFLDPSVSWFIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWKISIRGNRI 120
Cbl_NCTC    -----TAKGNFENAPEIAGASILLEFIPELLIPVVGAFLLSEYIDNKNKIITIDNALTNRNEKWSMDMYGLIVAQWLS-----TVNTQFYTIKEGMYKALNYQAQALEEII 101
              *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *

Smith8_186  IWTLLIDINGKTKSVFPFEYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVIANGEIIFKLDGDIIDRTQFIWM---KYFSIFNTELSQSNIERYKIQSYSEYLKDFW 237
Cbl_NCTC    KYRYNIYSEKEKS-----NINIDFND-INSKLNEGINQAIDNINNFINGCCSVSYLMKKMIPLAVEK---LLDPDNTLKKNLLNYIDENKLYLIGSAEYKSKVNK--YLTIMPPDLSTY 210
              *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *

Smith8_186  GNPLMYNKEYYMPNAGNKNYSYIKLKKDSPVGEILTRSKYNQNSKYINYRDLYIGEKFIIRKKSNSQSINDDIVRKEDYIYLDFFNLNQEWVRVYTYKYPKKEEEKLFLAPISDSDELYNTI 357
Cbl_NCTC    TNDFTLIEFNPKNYSEILN-NIILNRYKDNILDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIR---VTQNQNIIFNSVF---LDPSVSWFIRIPKYKNDGIQNYIHNEYTIINCM 323
              *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *

Smith8_186  QIKEYDEQPTYSCQLLPKKDEESTDEIGLIGIHRFYESGIVFEEYKDYFCISKWYLKEVKKRPYNLKLGCNWQFIPKDEGWTE 440
Cbl_NCTC    KNSGWKISIRGNRIIWT-----LIDINGKTKS--VFFEYN-----IRED----- 361
              *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *      *

```

### Alignment 10

Smith SEQ ID NO:8 (hereinafter "Smith8\_186") was aligned with the amino acid sequence of Halpern (as shown at p. 11189, col. 1, paragraph 4, line 2; hereinafter "Halpern"). Identical amino acids are marked by an asterix highlighted in yellow.

[illegible]

**Alignment 11**

Smith SEQ ID NO:7 (hereinafter "Smith7\_186") was aligned with the nucleotide sequence of Whalen (Accession M81186; hereinafter "M81186"). A preliminary alignment (not shown) with the full-length nucleotide sequence of Whalen M81186 revealed very little identity over approximately the first 2580 nucleotides. Therefore, this alignment is limited to only nucleotides 2581-4041. Selection of this region was haphazard with consideration given merely to providing some overlap on either end of the region of highest similarity. Identical nucleotides are marked by an asterisk highlighted in yellow.

```
Smith7_186 -----GAATTCACGATGGCCAAACAAATACAATTCGGAAATCCGTAACAAATCATCTCGAACCTGCGTTACAAAGACAACAAATCGATCGATCTGCTGGTTACG 100
M81186 TATATACCAATGATACAACTACTAATAGAAATGTTTAAATAAATATAATAGCGAAATTTTAAATAAATATTAATCTTAAATTTAAGATATAAGGATAAATAATTTAATAGATTTATCAGGATATG 2700
      * * * * *
Smith7_186 GTGCTAAAGTTGAAGTATACGACGGTGTGAACCTGAATGACAAGAACCAGTTCAAACTGACCTCTTCGCGTAACCTTAAGATCCGTGTTACTCAGAATCAGAATCATCTTCAACTCCG 220
M81186 GGGCAAAAGGTAGAGGTATATGATGGAGTCGAGCTTAATGATAAAATCAATTTAAATTAACCTAGTTTCAGCAAAATAGTAAGATTAGAGTGACTCAAAATCAGAATATCATATTTAATAGT 2820
      * * * * *
Smith7_186 TATTCCTGGACTTCTCTGTTCCTTCTGGATCCGTATCCCGAAATACAAGAACGACGGTATCCAGAATTACATCCACAATGAATACACCATCATCAACTGCATGAAGAATAAATCTGGTT 340
M81186 TGTTCCTTGTATTTAGCGTTAGCTTTTGGATAAAGATACCTAAATATAAGAATGATGGTATACAAAAATTATTTATCATATGAATATACAATAATTAATTTGTATGAAAAATAATTCGGGCT 2940
      * * * * *
Smith7_186 GGAAGATCTCCATCCCGGTAACCGTATCATCTGGACTCTGATCGATATCAACGGTAAGACCAAAATCTGTATTTCTCGAATACAACATCCGTGAAGACATCTCTGAATACATCAATCGCT 460
M81186 GGAAAAATATCTATTAGGGGTAAATAGGATAATATGGACTTTTAAATTTGATATAAATGGAAAAACCAATTCGGTATTTTGTGAATATAACATAAGAGAAGATATATCAGAGTATATAAATAGAT 3060
      * * * * *
Smith7_186 GGTTCCTCGTTACCATCACCAATAACCTGAACAATGCTAAAAATCTACATCAACGGTAAACTGGAATCTAATACCGACATCAAAGACATCCGTGAAGTTATCGCTAACGGTGAAATCATCT 580
M81186 GGTTTTTTTGTAAGTATTAATAATTTGAATAACGCTAAAAATTTATATTAATTTGTAAGCTAGAATCAATACAGATATTAAGATATAAGAGAAGTTATTTGCTAATGGTGAAATTAATAT 3180
      * * * * *
Smith7_186 TCAAACTGGACGGTGACATCGATCGTACCCAGTTTCATCTGGATGAAATACTTCTCCATCTTCAACACCGAACTGTCTCAGTCCAATATCGAAGAACGGTACAAGATCCAGTCTTACTCCG 700
M81186 TTAATTTAGATGCTGATATAGATAGAACACAAATTTATTTGGATGAAATATTTTCAGTATTTTAAATACGGAATTAAGTCAATCAAAATATTTGAAGAAAGATATAAAATTCATATAGCG 3300
      * * * * *
Smith7_186 AATACCTGAAAGACTTCTGGGGTAATCCGCTGATGTACAACAAAGAATACTATATGTTTCAATGCTGGTAAACAAGAACTCTTACATCAAACCTGAAGAAAGACTTCCGGTTGGTGAAATCC 820
M81186 AATATTTAAAGATTTTGGGGAAATCCCTTTAATGTACAATAAAGAATATATATGTTTAAATGCGGGGAATAAAATTCATATATTAAGATAAAGAAAGATTCACCTGTAGGTGAAATTT 3420
      * * * * *
Smith7_186 TGACTCGTTCCAAATACAACGAACTCTAAATACATCAACTACCGGACCTGTACATCGGTGAAAGTTTCAATCATCCGTCGCAAAATCAACTCTCAGTCCATCAATGATGACATCGTAC 940
M81186 TAACACGTAGCAAAATATAATCAAAATTTCTAAATATATAAATTTATAGAGATTTATATATTTGGAGAAAAATTTATTTAAGAAAGAAAGTCAAAATCTCAATCTATAAATGATGATATAGTTA 3540
      * * * * *
Smith7_186 GTAAAGAAGACTACATCTACCTGGACTTCTTCAACCTGAATCAGGAATGGCGTGTATACACCTACAAGTACTTCAAGAAAGAAGAAAGAAAGCTTTTCCCTGGCTCCGATCTCTGATTTCCG 1060
M81186 GAAAAGAAGATTATATATCTAGATTTTAAATTTAAATCAAGAGTGGAGATATATACCTATAAATATTTTAAAGAAAGAGGAAGAAATTTGTTTGTAGCTCTCTAAGTATTTCTG 3660
      * * * * *
Smith7_186 ACGAACTCTACAACACCATCCAGATCAAAAGAAATACGACGAACAGCGACCTACTCTTGCCAGCTGCTGTTCAAGAAAGATGAAGAAATCTACTGACGAAATCGGTCTGATCGGTATCCACC 1180
M81186 ATGAGTTTACAATACTATACAAATAAAAGAAATATGATGAACAGCCAACATATAGTTGTCTAGTTCTTTTAAAGAAAGATGAAGAAAGTACTGATGAGATAGGATTTGATTTGGTATTCATC 3780
      * * * * *
Smith7_186 GTTTCTACGAATCTGGTATCGTATTCGAAGAATACAAAGACTACTTCTGCATCTCCAAATGGTACCTGAAGGAAGTTAAACGCAAAACCGTACAACCTGAACTGGGTGCAATTTGGCAGT 1300
M81186 GTTTCTACGAATCTGGAAATGTATTTGAAGAGTATAAAGATTTATTTTGTATAAGTAAATGGTACTTAAAGAGGTAAAGAAAGCAACATATAATTTAAATTTGGGATGTAATTTGGCAGT 3900
      * * * * *
Smith7_186 TCATCCCGAAAGACGAAGTTGGACCGAATAGTAAGAATTC-----
M81186 TTATTCCTTAAAGATGAAGGTGGACTGAATAATAAATATATGCTCAGCAAACTATTTTATATAAGAAAGTTTAAAGTTTATAAAATCTTAAAGTTTAAAGATGTAGCTAAATTTTGAA 4020
      * * * * *
Smith7_186 -----
M81186 TATTAGATAAACTACATGTTT 1461
```



## Alignment 12

Smith SEQ ID NO:8 (hereinafter "Smith8\_186") was aligned with the amino acid sequence of Whalen (Accession M81186; hereinafter "M81186"). A preliminary alignment (not shown) with the full-length nucleotide sequence of Whalen M81186 revealed very little identity over approximately the first 840 amino acids. Therefore, this alignment is limited to only amino acids 841-1291. Selection of this region was haphazard with consideration given merely to providing some overlap on either end of the region of highest similarity. Identical amino acids are marked by an asterisk highlighted in yellow.

```

Smith8_186  -----MANKYNSEILNNIILNLRKYDNNLIDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIRVTQNQNIIFNSVFLDFSVSFWIRIPKYKNDGIQNYIHNEYTIINCMKNNS 109
M81186      SIYTNDTILIEMFNKYNSEILNNIILNLRKYDNNLIDLSGYGAKVEVYDGVELNDKNQFKLTSSANSKIRVTQNQNIIFNSVFLDFSVSFWIRIPKYKNDGIQNYIHNEYTIINCMKNNS 960
          *.....

Smith8_186  GWKISIRGNRIIWTLDINGKTKSVFPEYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVIANGEIIFKLDGDDIDRTQFIWMKYFSIFNTELSQSNIERYKIQSY 229
M81186      GWKISIRGNRIIWTLDINGKTKSVFPEYNIREDISEYINRWFFVTITNNLNNAKIYINGKLESNTDIKDIREVIANGEIIFKLDGDDIDRTQFIWMKYFSIFNTELSQSNIERYKIQSY 1080
          *.....

Smith8_186  SEYLKDFWGNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDLYIGEKFIIRKKSNSQSINDDIVRKEDYIYLDFFNLNQEWVRVYTYKYFKKEEEKLFLAPISD 349
M81186      SEYLKDFWGNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDLYIGEKFIIRKKSNSQSINDDIVRKEDYIYLDFFNLNQEWVRVYTYKYFKKEEEKLFLAPISD 1200
          *.....

Smith8_186  SDELYNTIQIKEYDEQPTYSCQLLPKKDEESTDEIGLIGIHRFYESGIVFEEYKDYFCISKWYLKEVKKRPYNLKLGCNWQFIPKDEGWTE 440
M81186      SDEFYNTIQIKEYDEQPTYSCQLLPKKDEESTDEIGLIGIHRFYESGIVFEEYKDYFCISKWYLKEVKKRPYNLKLGCNWQFIPKDEGWTE 1291
          *.....

```

**Alignment 13**

Smith SEQ ID NO:7 (hereinafter "Smith7\_186") was aligned with the nucleotide sequence of Jung (as shown at Jung, page 71, Figure 4A; hereinafter "Jung\_N-ter"). Identical nucleotides are marked by an asterisk highlighted in yellow.

```
Smith7_186      GAATTCACGATGGCCACAAATACAATTCGGAATCCTGAACAAATCATCCTGAACCTGCGTTACAAAGACAACAATCTGATCGATCTGTCTGGTTACGGTGTCTAAAGTTGAAGTATAC 120
Jung_N-ter      -----

Smith7_186      GACGGTGTGAACGTAATGACAAGAACCAGTTCAAAGTACCTCTCCGCTAACTCTAAGATCCGTGTACTCAGAATCAGAATCATCTTCAACTCCGTATTCCTGGACTTCTCTGTT 240
Jung_N-ter      -----

Smith7_186      TCCTTCTGGATCCGTATCCCGAAATACAAGAACGACGGTATCCAGAAATACATCCACAATGAATACACCATCATCAACTGCATGAAGAATAACTCTGGTTGGAAGATCTCCATCCGCGGT 360
Jung_N-ter      -----

Smith7_186      AACCGTATCATCTGGACTCTGATCGATATCAACGGTAAGACCAAACTGTATTCCTCGAATACAACATCCGTGAAGACATCTCTGAATACATCAATCGCTGGTTCTTCGTTACCATCACC 480
Jung_N-ter      -----

Smith7_186      AATAACCTGAACAAATGCTAAAATCTACATCAACGGTAAACTGGAATCTAATACCGACATCAAGACATCCGTGAAGTTATCGCTAACGGTGAAATCATCTTCAAACCTGGACGGTGACATC 600
Jung_N-ter      -----AAAGCTCCAGGAATATGTATTGATGTTGATAATGAA 36
                      ** * * * * *

Smith7_186      GATCGTACCCAGTTCATCTGGATGAAATACTTCTCCA----TCTTCAACACCGAACTGTCTCAGTCCAATATC--GAAGAACGGTACAAGATCCAGTCTTACTCCGAATACCTGAAAGAC 714
Jung_N-ter      GATT-TGTTCTTTTATAGCTGATAAAAAATAGTTTTCAGATTATCTAAAAACGAAAGAATAGAATATAATACACAGAGTAATTATAGAAAAATGACTTCCCTATAAAAT---GAATTAA 151
                      *** * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Smith7_186      TTCTGGGGTAATCCGCTGATGTACAACAAAGAACTACTATATGTTCAATGCTGGTAACAAGAACTCTTACATCAAACTGAAGAAAGACTCTCCGGTTGGTGAAATCCTGACTCGTTCCAAA 834
Jung_N-ter      TTTTAGA-----TACTGATTAAATAAGTAAATAGAAT-TACCAAGTGAAAAA-CAGAATCACTTAC--TGATTTTAATGTAGATGTTCCAGTATATGAAAAAC-AACCCGCTATAAA 260
                      * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Smith7_186      TACAACCAGAATCT-TAAATACATCAACTACCGGACCTGTACATCGGTGAAAAGTTCACTATCCGTGCAAAATCTAACTCTCAGTCCATCAATGATGACATCGTACGTAAGAAGACTA 953
Jung_N-ter      AAAAAATTTTACAGATGAAAAATACCATCTTTCAATATTTATACTC--TCAGACATTT-----
                      * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * * *

Smith7_186      CATCTACCTGGACTTCTTCAACCTGAATCAGGAATGGCGTGTATACACCTACAAGTACTTCAAGAAAGAAGAAGAAAAGCTTTTCTCTGGCTCCGATCTCTGATTCGGACGAACCTCTACAA 1073
Jung_N-ter      -----

Smith7_186      CACCATCCAGATCAAAGAATACGACGAACAGCCGACCTACTCTTGCAGCTGCTGTTCAGAAAGATGAAGAATCTACTGACGAAATCGGTCTGATCGGTATCCACCGTTTCTACGAATC 1193
Jung_N-ter      -----

Smith7_186      TGGTATCGTATTCGAAGAATACAAAGACTACTTCTGCATCTCCAAATGGTACCTGAAGGAAGTTAAACGCAACCGGTACAACCTGAAACTGGGTGCAATGGCAGTTTCATCCGAAAGA 1313
Jung_N-ter      -----

Smith7_186      CGAAGGTGGACCGAATAGTAAGAAATTC 1341
Jung_N-ter      -----
```

## Alignment 14

Smith SEQ ID NO:8 (hereinafter "Smith8\_186") was aligned with the amino acid sequence of Jung (as shown at Jung, page 71, Figure 4A; hereinafter "Jung\_N-ter"). The sequence shown in Jung Figure 4B is identical to Jung Figure 4A except residues shown in blue are omitted from Jung Figure 4B. Identical amino acids are marked by an asterix highlighted in yellow.

```

Smith8_186  MANKYNSEILNNIILNLRKDNLDLSGYGAKVEVYDGVELNDKNQPKLTSSANSKIRVTQNQNIIFNSVFLDFSVSFWIRIPKYKNDGIQNYIHNEYTIINCMKNNSGWKISIRGNRI 120
Jung_N-ter  -----KAPGICIDVDNEDLFFIADKNSFSN-----LSKNERIEYN-----NQSNYIENDFPINELILDTD----- 55
           *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
Smith8_186  IWTLLIDINGKTKSVFFPEYNIREDISSEYINRWFFVTITNNLWNAKIYINGKLESNTDIKDIREVIANGELIFPKLDGDDIDRTQPIWMKYFSIFNTELSQSNIERYKIQSYSEYKDFWGNP 240
Jung_N-ter  LISKIELPSENTESLTDNFVDVPVYEKQ-----PAIKKIPTDENTIP-----QYLYSQTF----- 105
           *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *   *
Smith8_186  LMYNKEYYMPNAGNKNSYIKLKKDSPVGEILTRSKYNQNSKYINYRDLYIGEKFIIIRKKSNSQSINDDIVRKEDYIYLDFFNLNQEWVRVYTYKYPKKEEEKLFLAPISDSDELYNTIQIK 360
Jung_N-ter  -----
Smith8_186  EYDEQPTYSCQLLFKKDEESTDEIGLIGIHRFPYESGIVFEEYKDYFCISKWYLKEVKKRPYNLKLGCNWQFIPKDEGWTE 440
Jung_N-ter  -----

```

**Alignment 15**

Smith SEQ ID NO:7 (hereinafter "Smith7\_186") was aligned with the nucleotide sequence of SEQ ID NO:22 of Williams (hereinafter "Will22\_665"). Identical nucleotides are marked by an asterix highlighted in yellow.

```
Smith7_186 -----GAATTCACGATGCGCAACAATAACAATCCGAAATCCTGAACAATATCATCCTGAACCTGCGTTACAAAGACAACAATCTGATCGATCTGCTGGTTACGGTGTCTAAAGTT 111
Will22_665 ATGGCTCGTCTGCTGCTACCTTTCACCTGAATACATCAAGAATCATCAATACCTCCATCCTGAACCTGCGGTACGAATCCAATCACCTGATCGACCTGCTCGCTACGGTTCCTCAAAATC 120
      * * * * *

Smith7_186 GAAGT--ATACGACGGTG---TTGAACTGAATGACAAGAACCAGTTCAAACCTGACCTCTCCGCTAACTCTAAGATCCGTTGTTACTCAGAATCAGAACATCATCTTCAACTCCGTTATTC 225
Will22_665 AACATCGGTTCTAAAGTTAACTTCGATCCGATCGACAAGAATCAGATCCAGCTGTTCAATCTGGAATCTTCCAAAATCGAAGTTATCTGGAAGATGCTATCGTATACAACTCTATGTAC 240
      * * * * *

Smith7_186 CTGGACTTCTCTGTTTCTCTCTGGAATCCGATATCCCGAAATACAAGAACGACGGTATCCAGAATTACATCCACAATGAATACACCATCATCAACTGCATGAAGAATAAATCTGGTTGGAAG 345
Will22_665 GAAAACCTTCTCCACCTCTCTCTGGATCCGATATCCCGAAATACTTCAACTCCATCTCTCTGAA-----CAATGAATACACCATCATCAACTGCATGGAAGAAATCTGGTTGGAAG 351
      * * * * *

Smith7_186 ATCTCCATCCGCGGTAAACCGTATCATCTGGACTCTGATCGATATCAACGGTAAGACCAAAATCTGTATTTCTGGAATACAACATCCGTTGAA--GACATCTCTGAATACATCAATCCGTTGGTT 464
Will22_665 GTATCTCTGAACCTACGGTGAATATCATCTGGACTCTGCGAGGACACTCAGGAAATCAAACAGCGGTGTTGTATTTCAAATACT-CTCAGATGATCAACATCTCTGACTACATCAATCCGTTGGAT 470
      * * * * *

Smith7_186 CTTCTGTTACCATCACCAATAACC--TGAACAATGCTAAAATCTACATCAACGGTAAACCTGG--AATCTAATACCGACATCAAGACATCCGTGAAGTTATCGCTAAACGGTGAAATCATC 579
Will22_665 CTTCTGTTACCATCACCAACAATCGCTGAATAACTCCAAAATCTACATCAACGGCGCTCTGATCGACAGAACCGATCTCCA--ATCTGGGTAACTCCACCGTTCTAATAACATCATC 588
      * * * * *

Smith7_186 TTCAAACCTGGACGGTGACATCGATCGTACCCAGTTTCATCTGGATGAAATACTTCTCCATCTTCAACACCGAACTGTCTCAGTCCAATATCGAAGAACGGTACAAGATCCAGTCTTACTCC 699
Will22_665 TTCAAACCTGGACGGTTGTCGTGACACTCACCGTACATCTGGATCAAAATCTTCAATCTGTTTCGACAAAGAACTGAACGAAAAAGAAATCAAGACCTGTACGACAACCAAGTCCAAATCT 708
      * * * * *

Smith7_186 GAATACCTGAAAGACTTCTGGGGTAATCCGCTGATGTACAACAAAGAACTACTATATGTTCAATGCTGGTAAACAAGAACTCTTACATCAAACTGAAGAAGACTCTCCGGTTGGTGAAAT- 818
Will22_665 GGTATCTTGAAGACTTCTGGGGTACTACCTGCAGTACGACAAACCGTACTACATGCTGAATCTGTACGATCCGAACAAATACGTTGACGTCAACAATGTAGGTATCCGCGGTTACATG 828
      * * * * *

Smith7_186 --CCTGACTCGTTCCAA--ATACAACCAGAACTCTAAATACAT-CAACTACCGGACCTGTACATCGGTGAAAGTTTATCATCCGTCGCAAAATCTAACTCTCAGTCCATCAATGATGAC 933
Will22_665 TACCTGAAAGGTCGCGGTGTTCTGTTATGACTACCAACATCTACCTGAACTCTTCCCTGTACCGTGGTACCAAAATTCATCATCAAG---AAATACGCGTCTGG---TAACAAGGACAAT 942
      * * * * *

Smith7_186 ATCGTACGTAAGAAGACTACATCTACCTGGACTTCTTCAACCTGAATCAGGAATGGCGGTGTATACACCTACAAGTACTTCA-AGAAAGAAGAAGAAAGCTTTTCTCGGCTCCG---AT 1049
Will22_665 ATCGTTCGCAACAAATGATCGTGTATACATCAATGTTGTAGTTAAGAACAAGAAATACCGTCT---GGCTACCAATGCTTCTCAGGCTGGTGTAGAAAGATCTTGCTGCTCTGGAAT 1058
      * * * * *

Smith7_186 CTCTGATTCGACGAACTCTACAACACCATCCAGATCAAAGAATACGACGAACAGCCGACCTACTCTTGCCAGCTGCTGTTCAAGAAAGATGAAGAATC-TACTGACGAAATCGGTCTGA 1168
Will22_665 CCCGGACGTTGGTAATCTGTCTCAGTAGTTGTAATGAAAT---CCAAGAACGACAGGGTATCACTAACAATGCAAAATGAATCTGCAGGACAACAATGGTAACGATATCGGTTTCA 1174
      * * * * *

Smith7_186 TCGGTATCCACCGTTTCTACGAATCTGGTATCGTATTTCAAGAAATACAAAGACTACTTCTGCATCTCCAAATGGTACCTGAAGGAAGTTAAACGCAAAACCGTACAACCTGAAACTGGGTT 1288
Will22_665 TCGGTTTCCACCACTTCAACAA-----TATCGC-----TAAACTGGTTGCTTC-----CAACTGGTACAATCTGCAGATCGAAGCTTCTCTCGCACTCTG-----GGTT 1264
      * * * * *

Smith7_186 GCAATTTGGAGTTTCATCCCGAAAGACGAAGGTTGGACCGAATA---GTAAGAATTC-----
Will22_665 GCTCTTGGGAGTTTCATCCCGGTTGATGACGGTTGGGGTGAACGCTCCGCTGTAACCCGGGAAAGCTT 1330
      * * * * *
```

## Alignment 16

Smith SEQ ID NO:8 (hereinafter "Smith8\_186") was aligned with the amino acid sequence of SEQ ID NO:23 of Williams (hereinafter "Will23\_665"). Identical amino acids are marked by an asterix highlighted in yellow.

```

Smith8_186  MA-----NKYNSEILNNIILNLRKDNLDLSGYGAKVEVDGVELN--DKNQPKLTSSANSKIRVTQNQNIIFNSVFLDFSVSWIRIPKYKNDGIONYIHNEYTIINCMKNNSGWK 112
Will23_665  MARLLSTPTEYIKNIINTSILNLRYESNHLIDLSRYASKINIGSKVNPDPIDKNQIQLFNLESSKIEVILKNAIVYNSMYENFSTSFWIRIPKYFN-SIS--LNNEYTIINCMENNSGWK 117
          * * * * *
Smith8_186  ISIRGNRIIWTLDIDNGKTKSVFFEYNIREDISSEYINRWPFVTITNN-LNNAKIYINGKLESNTDIKDIREVIANGEIIFKLDGDIQFQIWMKYFSIFNTELSQSNIEERYKIQSYSE 231
Will23_665  VSLNYGEI IWTLDQTQEIQRVVFVKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPISNLGNHASNNIMFKLDGCRDTHRYIWKYFNLFDKELNEKEIKDLYDNQNSNG 237
          * * * * *
Smith8_186  YLKDFWGNPLMYNKEYYMFNAGNKNSYIKLKKDSPVGEILT---RSKYNQNSKYINVRDLYIGEKFIIIRKKSNSQSINDDIVRKEDYIYLDFFNLNQEWVRVYTYKYFKKEEKLFLAPIS 348
Will23_665  ILKDFWGDYLYDKPYMYMLNLYDPNKYVDVNNVGIRGYMYLKGPRGSVMTTNIYLS-SLYRGTKFIIKKYASGN--KDNIVRNNDRVYINNVVKNKEYRLATNASQAGVEKILSALEIP 354
          * * * * *
Smith8_186  DSDELYNTIQIKEYDEQ-PTYSCQLLFKKDEESTDEIGLIGIHRFYESGIVFEEYKDYFCISKWYLKEVKKRPYNLKLGCNWQFIPKDEGWTE--- 440
Will23_665  DVGNLQVVMKSKNDQGITNKCKMNLQ--DNNGNDIGFIGFHQFNN-----IAKLVASNWNRYNRIERSSR--TLGCSWEFIPVDDGGERPL 438
          * * * * *

```

**Alignment 17**

Smith SEQ ID NO:7 (hereinafter "Smith7\_186") was aligned with the nucleotide sequence of SEQ ID NO:25 of Williams (hereinafter "Will25\_665"). Identical nucleotides are marked by an asterix highlighted in yellow.

```
Smith7_186 -----GAATTCACGATGGCCAAACAAATACAATTCGAAATCTCG 39
Will25_665 ATGGGCCATCATCATCATCATCATCATCATCACAGCAGCGCCATATCGAAGTCGTCATATGGCTAGCATGGCTCGTCTGCTTACCTTCACTGAATACATCAAGAACATCATC 120
          * * * * *

Smith7_186 AACAAATATCATCTGAACCTGCGTTACAAAGACAACAAATCGATCGATCTGTCTGGTTACGGTGCTAAAGTTGAAGT--ATACGACGGTG---TTGAAGTGAATGACAAGAACCAGTTTC 153
Will25_665 AATACCTCCATCTGAACCTGCGTTACGAATCCAATCACCTGATCGACCTGTCTCGCTACGCTTCCAAATCAACATCGGTTCATAAGTTAACTTCGATCCGATCGACAAGAATCAGATC 240
          * * * * *

Smith7_186 AAACCTGACCTCTTCGCTTAACCTTAAGATCCGTGTACTCAGAATCAGAACATCATCTTCAACTCCGTATTCCTGGACTTCTCTGTTCCTTCGGATCCGATCCCGAAATACAAGAAC 273
Will25_665 CAGCTGTTCAAATCTGGAATCTTCCAAATCGAAGTTATCTCTGAAGAAATGCTATCGTATACAACTATGTACGAAAACTTCTCCACCTCCTTCGGATCCGATCCCGAAATACTTCAAC 360
          * * * * *

Smith7_186 GACGGTATCCAGAAATACATCCCAATGAAATACACCATCATCAACTGCAATGAAGAATAAATCTGGTTGGAAGATCTCCATCCGCGGTAAACCGTATCATCTGGACTTCGATCGATATCAAC 393
Will25_665 TCCATCTCTCTGAA-----CAATGAATACACCATCATCAACTGCAATGGAAGAACTTCTGGTTGGAAGATCTCTGAACTACGGTGAAATCATCTGGACTTCGACGAGACTCAG 471
          * * * * *

Smith7_186 GGTAAAGCAAAATCTGTATCTTCGAATACAACATCCGTGAA--GACATCTCTGAATACATCAATCGCTGGTTCTTCGTTACCATCACCAATAACC---TGAACAAATGCTAAAACTTACAT 509
Will25_665 GAAATCAAAACAGCGTGTGTATTCAAATACT--CTCAGATGATCAACATCTCTGACTACATCAATCGCTGGATCTCTGTTACCATCACCAACATCGCTGAAATACTCCAAATCTACAT 590
          * * * * *

Smith7_186 CAACGGTAAACTGG--AATCTAATACCGACATCAAGACATCCGTGAAGTTATCGCTAACGGTGAAATCATCTTCAAACTGGACGGTGACATCGATCGTACCCAGTTTATCTGGATGAAA 627
Will25_665 CAACGGCGCTGATCGACGAGAAACCGATCTCCA--ATCTGGGTAAATCCACGCTTCTAAATAACATCATGTTCAAACTGGACGGTTGCTGACACTCACCGCTACATCTGGATCAAA 708
          * * * * *

Smith7_186 TACTTCTCCATCTTCAACACCGAACTGTCTCAGTCCAATATCGAAGAACGGTACAAGATCCAGTCTTACTCCGAATACCTGAAAGACTTCTGGGGTAAATCCGCTGATGTACAACAAAGAA 747
Will25_665 TACTTCAATCTGTTCGACAAAGAACTGAACGAAAGAAATCAAGACCTGTACGACAAACAGTCCAATTCCTGGTATCTCTGAAAGACTTCTGGGGTGACTACTTCGAGTACGACAAACCG 828
          * * * * *

Smith7_186 TACTATATGTTCAATGCTGGTAAACAGAACTTTACATCAAACTGAAGAAAGACTTCTCCGGTTGGTGAAAT---CCTGACTCGTTCCAA--ATACAACGAGAACTTAAATACAT--CAAC 861
Will25_665 TACTACATGCTGAATCTGTACGATCCGAAACAAATACGTTGACGTCAACAAATGTAGGTATCCCGGGTTACATGTACCTGAAAGTCCGCGTGGTTCTGTATGACTACCAACATCTACCTG 948
          * * * * *

Smith7_186 TACCGGACCTGTACATCGGTGAAAAGTTTATCATCCCTCGCAAAATCTAACTCTCAGTCCATCAATGATGACATCGTACGTAAAGAAGACTACATCTACCTGGACTTCTTCAACCTGAAAT 981
Will25_665 AACTCTTCCCTGTACCGTGGTACCAATTCATCATCAAG---AAATACGCGTCTGG---TAACAAGGACAATATCGTTCGCAACAATGATCGTGTATACATCAATGTGTAGTTAAGAAC 1062
          * * * * *

Smith7_186 CAGGAATGGCGTGATACACCTACAAGTACTTCA--AGAAAGAAGAAGAAAGCTTTCTCTGGCTCCG---ATCTCTGATTCGACGAACTCTACAACACCATCCAGATCAAGAAATACGA 1097
Will25_665 AAAGAATACCGTCT---GGCTACCAATGCTTCTCAGGCTGGGTAGAAAAGATCTTGTCTGCTCTGGAAATCCCGGACGTGGTAAATCTGTCTCAGGTAGTTGTAATGAAAT---CCA 1174
          * * * * *

Smith7_186 CGAACAGCCGACCTACTCTTCCAGCTGCTGTTCAGAAAGATGAAGAATC--TACTGACGAAATCGGTCTGATCCGGTATCCACCGTTTCTACGAATCTGGTATCTGTATTCGAAGAATACA 1216
Will25_665 AGAACGACCGGGTATCACTTAACAAATGAAAAATGAATCTGCAGGACACAACATGGTAACGATATCGGTTTCAATCGGTTTCCACCAAGTTCAACAA-----TATCGC-----TAAA 1278
          * * * * *

Smith7_186 AAGACTACTTCTGCATCTCCAATGGTACCTGAAGGAAGTTAAACGCAAAACCGTACAACC TGAAACTGGGTGCAATTTGGCAGTTTATCCGAAAGACGAAGTTGGACCGAATA---GT 1333
Will25_665 CTGGTTGCTTC-----CAACTGGTACAATCTGATGATCGAAGCTTCTCTCTGCACCTC TG-----GGTTGCTCTTGGGAGTTTATCCCGGTTGATGACGGTTGGGGTGAACGTCCTCG 1384
          * * * * *

Smith7_186 AAGAAATTC----- 1341
Will25_665 TGTAAACCCGGAAAGCTT 1402
          * * *
```

## Alignment 18

Smith SEQ ID NO:8 (hereinafter "Smith8\_186") was aligned with the amino acid sequence of SEQ ID NO:26 of Williams (hereinafter "Will26\_665"). Identical amino acids are marked by an asterix highlighted in yellow.

```

Smith8_186 -----MA-----NKNSEILNNIILNRYKDNMLIDLSCYGAKVEVYDGVELN--DKNQPKLTSSANSKIRVTQNNQNIIFNSVPLDPSVSPWIRIPKYKN 88
Will26_665 MGHHHHHHHHHSSGHIEGRHMASMARLLSTFTEYIKNIINTSILNLYESNHLIDLSRYASKINIGSKVNFDPIDKNQIQLFNLESSKIEVILKNAIVVNSMYENFSTSFWIRIPKYFN 120
          * * * * *
Smith8_186 DGIQNYIHNEYTIINCMKNNSGWKISIRGNRIIWTLIDINGKTKSVFFEYNIREDISEYINRWFFVTITNN-LNNAKIYINGKLESNTDIKDIREVIANGEIIFKLDGDDIDRTQFIWMKY 207
Will26_665 -SIS--LNNEYTIINCMENNSGWKISLNYGEIITLQDTQEIQRVVFYKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPISNLGNHASNNIMFKLDGCRDTHRYIWKY 237
          * * * * *
Smith8_186 PSIFNTELSQSNIEERYKIQSYSEYKDFWGNPLMYNKEYYMFNAGNKNYSYIKLKDSPVCEILT---RSKYNQNSKYINYRDLVIGKFIIRKKSNSQSINDDIVRKEDYIYLDFFNLN 324
Will26_665 FNLFDKELNEKEIKDLYDNQNSGILKDFWGDYLDKPYMYMLNLYDPNKYVDVNVGIRGYMYLKGPRGSVMTTNIYLSN-SLYRGTKFIIKKYASGN--KDNIVRNDRVYINVVVK 354
          * * * * *
Smith8_186 QEWRVYTYKYFKKEEEKLFLAPISDSDELYNTIQIKEYDEQ-PTYSCQLLFKKDEESTDEIGLIGIHRFYESGIVFEYKDYFCISKWYLKEVKRKPYNLKLGCNWFIPKDEGWTE--- 440
Will26_665 KEYRLATNASQAGVEKILSALEIPDVGNLSQVVVMKSKNDQGITNKCKMNLQ--DNNGNDIGFIGFHQFNN-----IAKLVASNWNRYNRQIERSSR--TLGCSWEFIPVDDGWGERPL 462
          * * * * *

```

**Alignment 19**

Smith SEQ ID NO:7 (hereinafter "Smith7\_186") was aligned with the nucleotide sequence of SEQ ID NO:27 of Williams (hereinafter "Will27\_665"). A preliminary alignment (not shown) with the full-length nucleotide sequence of Will27\_665 revealed very little identity over approximately the first 2520 nucleotides. Therefore, this alignment is limited to only nucleotides 2521-3891. Selection of this region was haphazard with consideration given merely to providing some overlap on either end of the region of highest similarity. Identical nucleotides are marked by an asterix highlighted in yellow.

```

Smith7_186 -----GAATTCACGATGGCCAACAAATACAAATTCGAAATCCTGAACAATATCATCTGAAC 57
Will27_665 GTTAATAATACACTTAGTACAGATATACCTTTTCAGCTTTCCAATACGTAGATAATCAAGATTATTATCTACATTTACTGAATATATTAAGAATATTATTAATCTCTATATTGAAT 2640
          * * * * *

Smith7_186 CTGCGTTACAAAGACAACAATCTGATCGATCTGCTGGTTACGGTGTCAAAGTTGAAGT--ATACGACGGTG---TTGAACTGAATGACAAGAACCAGTTCAAACCTGACCTTCCGCT 171
Will27_665 TTAAGATATGAAAGTAATCATTTAATAGACTTATCTAGGTATGCATCAAAAATAAATATTGGTAGTAAAGTAAATTTTGATCCAATAGATAAAAAATCAAATTCATTTAATTTAGAA 2760
          * * * * *

Smith7_186 AACTCTAAGATCCGTGTTACTCAGAAATCAGAACATCATCTTCAACTCCGTATTCCTGGACTTCTCTGTTTCCCTTCTGGATCCGTATCCCGAAATACAAGAACGACGGTATCCAGAAATPAC 291
Will27_665 AGTAGTAAATTTGAGGTAAATTTTAAAAAATGCTATTGTATATAATAGTATGTATGAAAATTTTAGTACTAGCTTTTGGATAAGAATTCCTAAGTATTTTAAACAGTATAAGCTTAAAT--- 2877
          * * * * *

Smith7_186 ATCCACAATGAATACACCATCATCAACTGCATGAAGAATAACTCTGGTTGGAAGATCTCCAATCCGCGGTAAACCGTATCATCTGGACTCTGATCGATATCAACGGTAAGACCAAACTGTGA 411
Will27_665 -----AATGAATATACAAATAAATAATTTGTATGGAATAAATTCAGGATGGAAGTATCACTTAATTATGGTGAAATAATCTGGACTTTACAGGATCTCAGGAAATAAAACAAAGAGTA 2991
          * * * * *

Smith7_186 TTCTTCGAATACAAATCCGTGAAGACATCTCGAATACATCAATCGCTGGTTCTTCGTTACCATCACCAATAAC---CTGAACAATGCTAAATCTACATCAACGGTAAACTGG--AAT 526
Will27_665 GTTTTTAAATACAGTCAAAATGATTAATATATCAGATTATATAAAGAGATGGATTTTTGTAACTATCACTAATAATAGATTAATAAATCTAAATTTATATAATGGAAGATTAAATAGAT 3111
          * * * * *

Smith7_186 CTAATACCGACATCAAGACATCCGTGAAGTTATCGCTAACGTTGAAATCACTTCAAACTGGACGGTGACATCGATCGTACCCAGTT-CATCTGGATGAAATACTTCTCCATCTTCAAC 645
Will27_665 CAAAAACCAATTTCAA--ATTTAGGTAAATTCATGCTAGTAATAATATAATGTTTAAATAGATGGTTGTAGAGAT-ACACATAGATATATTGGATAAAATATTATTAATCTTTTGTAT 3228
          * * * * *

Smith7_186 ACCGAATGCTCTCAATATCGAAGAACGGTACAAGATCCAGTCTTACTCCGAATACCTGAAAGACTTCTGGGGTAATCCGCTGATGTACAACAAGAACTATATGTTCAATGCT 765
Will27_665 AAGGAATTAATGAAAGAAATCAAGATTATATGATAATCAATCAAAATTCAGGTATTTTAAAGACTTTTGGGGTGAATTATTACAATATGATAAACCATATCTATGTTAAATTTA 3348
          * * * * *

Smith7_186 GGTAACAAGAACTCTTACATCAAACTGAAGAA---AGACTCTCCGGTTGGTGAAATCCTGACTCGTTCCAATACAAACGAACTCTAAATACATCAACT---ACCGCGACCTGTACATC 879
Will27_665 TATGATCCAATAAATATGTCGATGTAATAATGTAGGTATATAGAGTTATATGTATCTTAAAGGGCTAGAGGTAGCGTAATGACTACAAACATTATTTTAAATTCAGATTGTATAGG 3468
          * * * * *

Smith7_186 GGTGAAAAGTTCATCCTCGTCAAAATCTAACTCTAGTCCATCAATGATGACATCGTACGTAAGAAAGACTACATCTACCTGGACTTCTTCAACCTGAATCAGGAATGGCGGTATAC 999
Will27_665 OGGACAAAATTTATATATAA---AAATATGCTTCTGGA---AATAAAGATAATATTGTTAGAAATAATGATCGTATATTAATGATAGTGTAAAAATAAAGAAATAGGTTAGCT 3582
          * * * * *

Smith7_186 ACCTACAAGTACTTCAAGAAAGAAGAAAGCTTTTCTGGCTCCGA--TCTCTGATTCCGACGAACTCTACAACACCAATCCAGATCAAGAAATACGACGAACAGCCGACCTACTCTT 1117
Will27_665 ACTAAT--GCATCACAGCGAGCGTAGAAAAATACTAAGTCAATTAGAAATACCTGATGTAG--GAAATCTAAGTCA--AGTAGTAGTAATGAAGTCAAAAAATGATCAAGGAATAACA 3696
          * * * * *

Smith7_186 GCCAGCTGCTGTTCAAGAAAGATGAAGAACTTACTGACGAAATCCGCTGATCGGTATCCACCGTTTCTACGAATCTGGTATCGTATTCGAAGAATACAAAGACTACTTCTGCATCTCCA 1237
Will27_665 AATAAATGC-----AAATGAA---TTTAC--AAGATAAATGGGAATGATATAGGC--TTTATAGGATTTC---ATCAGTTTAATATATAGCTAAACTAGTAGCAAGT---A 3792
          * * * * *

Smith7_186 AATGGTACCTGAAGGAAGTTAAACGCAACCGTACAACCTGAAACTGGGTTGCAATTGGCAGTTTCAATCCCGAAAGACGAAGGTTGGACCGAATAGTAAGAATTC 1341
Will27_665 ATTGGTATAATAGACAAATAGAAAAG-ATCTAGTAGGACTT-----TGGGTTGCTCATGGGAAATTTATCTCTGTAGATGATGGATGGGAGAAAGGCCACTGTAA 3890
          * * * * *

```



## Alignment 20

Smith SEQ ID NO:8 (hereinafter "Smith8\_186") was aligned with the amino acid sequence of SEQ ID NO:28 of Williams (hereinafter "Will28\_665"). A preliminary alignment (not shown) with the full-length amino acid sequence of Will28\_665 revealed very little identity over approximately the first 840 amino acids. Therefore, this alignment is limited to only amino acids 2521-3891. Selection of this region was haphazard with consideration given merely to providing some overlap on either end of the region of highest similarity. Identical amino acids are marked by an asterix highlighted in yellow.

Smith8\_186 -----MANKYNSEILNNIILNRYKDNMLIDLSGYGAKEVYDGVELN--DKNQFKLTSSANSKIRVTQNQNIIFNSVFLDFSVSWFIRIPKVKYNDGIQNY 94  
Ophd28\_665 VNNTLSTDIPQLSKYVDNQRLSTPTPEYIKNIINTSILNRYESNHLIDLSRYAKSINIGSKVNPDPIDKQIQLPNLESSKIEVILKNAIVYNSYENFSTSWFIRIPKYPFN--SIS-- 957  
\*\*\*\*\*  
Smith8\_186 IHNEYTIINCMMKNNSGWKISIRGNRIIWTFLIDINGKTSVFPPEYNIREDISeyINRWFFVTITNN-LNNAKIYINGKLESNTDIKDIREVIANGEEIFKLDGIDRDTQPIWMKYFSIFNT 213  
Ophd28\_665 LNNEYTIINCMEKNNSGWKISLNYGEIITWLODQTQBIKQVRVFKYSQMINISDYINRWIFVTITNNRLNNSKIYINGRLIDQKPISNLGNIAHSNNIMFKLDGCDRDTHRYIWIKYFNLPDK 1077  
\*\*\*\*\*  
Smith8\_186 ELSQSNIEERYKIQSYSEYKLDKDFGNPLMYNKKEYMFPAGNKNSEYIKLKKDSPVGEILT---RSKYNQNSKYINRYDLIGEKFIIRRKNSQSINDDIVRKEDYIYLDFFNLNQEWRYV 330  
Ophd28\_665 ELNEKEIKDLVDNQNSGILKDFWGDYLDYQDKPYMYLNLDPNKYVDVNNVGRIGYMYLKGPRGSVMPTNIYLSN-SLYRGTKFIIKKYASGN--KDNIVRNDRVYINVVVKNKERYLA 1194  
\*\*\*\*\*  
Smith8\_186 TYKYPKKBEKKFLAPISDSDELYNTIQIKEYDEQ--PTYSQCLLPKKDEESTDEIGLGIHRFPYESGIVPEEYKDYFCISKWYLKEVKRKPYNLKLGCNQWIPKDEGWTE--- 440  
Ophd28\_665 TNAQAGAVEKILSALEIPDVGNLSQVVVMKSKNDQGITNCKCKMNLQ--DNGNDIGTGFIPGHQFNN-----IAKLVASNNYNRQIERSR--TLGCSWPEIPVDGDGWERPL 1296  
\*\*\*\*\*